NUCLEOPLASTY

A new treatment option for cervical radicular pain due to a disc herniation

Judith Divera de Rooij

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Nucleoplasty
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Nucleoplastie
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Voor mijn ouders

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Chapter one

INTRODUCTION AND OUTLINE THESIS

Introduction

Cervical radicular pain (CRP) due to a disc herniation is a common condition, which, with neurological disorders, can be extremely painful and largely impact one's daily functioning and quality of life[1]. A wide range of nonsurgical and surgical interventions are used with major impacts on direct and indirect healthcare costs, making it a highly relevant topic. A new minimally invasive approach (i.e., nucleoplasty) is becoming increasingly popular among interventional pain specialists as one of the therapeutic options for the treatment of CRP due to a disc herniation. This thesis focuses on the efficacy and safety of this new treatment option in comparison to conservative and surgical treatments for patients with CRP due to a disc herniation.

Cervical radicular pain due to a disc herniation

There is no uniform definition of CRP due to a disc herniation. Aside from this, many other terms such as cervicobrachial pain, cervical radiculitis, cervical radiculopathy or cervical radicular syndrome are used in the literature for CRP as well.[2,3] In this thesis, we defined CRP due to a disc herniation as pain perceived in the upper limb, shooting or electric in quality, caused by irritation and or injury of a cervical spinal nerve.[4] The clinical presentation of CRP is vague, it has a wide range of subjective descriptions of the character of the pain. Moreover, the anatomic distribution of CRP is highly variable because there is a wide overlap and considerable variability of dermatomes between individuals.[4]

At present, there is a lack of epidemiological data of CRP due to a disc herniation, however some data of cervical radiculopathy (CR) and its risk factors have been described.[5] A door-to-door survey in a Sicilian municipality reported a prevalence of 3.5 per 1000 persons[6] and with increasing age the risk of developing CR increases.[6,7] In a recently published epidemiological review within the population of the United States military (2000-2009) the incidence of CR was 1.79 per 1000 persons.[8] The incidence was calculated from a prospectively collected military database which is based on over 20,000 instances within an ethically and socioeconomically diverse cohort. The annual incidence rate was 1.76 per 1000 for men and 1.95 per 1000 for women.[8] Age is most likely the greatest risk factor for developing CR and females are at greater risk than males.[6-8]

Pathofysiology

Two mechanisms might cause CRP: nucleus pulposus material leaking onto the cervical spinal nerve root and/or compression of the cervical spinal nerve root by anatomic abnormalities.[9] It is hypothesised that a disc herniation leads to leakage of various inflammatory mediators and immunologic factors, which produce neural inflammation and, hence, an excitation of the nociceptors.[9] Once sensitized, the mechanical compression can cause pain.[9] The extent of the neural inflammation and

immune responses is related to the magnitude of the mechanical stimulus.[9] Thus, there is a complex link between mechanical deformation, neural inflammatory and central neuroimmune responses that together initiate and maintain radicular pain.[10]

Diagnosis

As in most pain syndromes, there is no gold standard for the diagnosis of CRP. A thorough history and physical examination are the cornerstones of the diagnosis. Magnetic resonance imaging (MRI) can be added for diagnosis to exclude primary pathologies such as tumor, infection, and fractures.[4] An MRI is also more suitable to reveal changes in the intervertebral discs, the spinal cord, the nerve roots, and its surrounding tissue[4]. When an MRI is inconclusive selective nerve root blocks[4] and electromyography (EMG) can be a valuable tool to localize the affected nerve root.[4,5]

Conservative treatment

Even though most patients with CRP are initially treated conservatively, little is known about the effectiveness of conservative care such as physiotherapy, manual therapy, immobilization, traction, nonsteroidal anti -inflammatory drugs (NSAIDs) and cervical steroid injection. The overall level of quality of evidence of physiotherapy, manual therapy, immobilisation and traction in patients with CR is low to very low, and not any of these interventions seems to be superior or consistently more effective than the other interventions.[11-13] Although, one might expect a positive effect of NSAIDs in the acute phase of CRP, we could not find evidence for that. Very low-level quality of evidence was found that a cervical epidural steroid injection is effective in pain relief for patients with CRP due to a disc herniation or degenerative spondylosis.[14] Although, the level of evidence of these conservative treatments is low to very low this does not imply that it is ineffective. It rather implies that the current body of evidence is insufficient to draw strong, precise conclusions, and that further study is needed.

The natural course of CR with conservative treatment appears to be long.[15] A recently performed cohort study of patients with CR who received conservative treatment found that 42% of the patients recovered from neck pain and 59% of the patients reported no or only slight arm pain at 6 months.[15] At 12 months, approximately half of the patients (47%) recovered from both neck pain and arm pain.[15] They also found that patients with longer duration of symptoms, i.e. 12 months, have a poorer course of recovery.[15] Another systematic review found that approximately 83% of the patients with CR completely recovered after 24 to 36 months with conservative treatment.[16] A small proportion of patients appear to have residual impairments, such as pain and activity limitations.[17] However, exact percentages of patients who suffer from a recurrent course are unknown.[17] When the severe pain persists and does not improve with conservative treatment surgical management is considered.

Surgical management

In general, there are two surgical approaches to treat CRP due to a disc herniation: 1) the anterior approach through the front of the neck and 2) the posterior approach through the back of the neck.[18,19] In the 1940s and the 1950s the posterior cervical foraminotomy (PCF) and the anterior cervical discectomy (ACD) with fusion (ACDF) techniques were developed and have been modified since then.[18] They are accepted and effective treatments for patients with CRP.[18-20]

Compared to PCF, ACD(F) has the advantage of wider access of disc space, i.e. direct decompression of the anterior offending structures by removing the intervertebral disc entirely along with any osteophytes at the posterior aspect of the vertebral body, bilateral decompression and importantly, less patient discomfort[18,19]. However, there are also disadvantages of an anterior approach, including symptomatic adjacent level disease, pseudoarthrosis, mechanical (device-related) failure and ventral approach related complications such as dysphagia, hematoma, and recurrent laryngeal nerve palsy.[18,19,21,22]

These disadvantages are not present with posterior cervical foraminotomy (PCF), which can provide better access to laterally positioned discs and is often less technically challenging.[18,19] Use of PCF can avoid ventral approach-related complications and does not require fusion, which avoids fusion-related complications.[18,19] Furthermore, PCF may also allow loose disc fragments to be removed.[19] Finally, with a posterior approach the patient also avoids the risks of damage to vital structures, i.e. trachea, oesophagus, sympathetic chain, internal carotid artery, vertebral artery and recurrent laryngeal nerve.[19] Disadvantages of this approach are that it is associated with limited surgical view of the distal foramen, difficulty in resecting osteophytes and increased epidural bleeding.[23] It also has a higher incidence of postoperative muscle spasm, neck pain and longer recovery time than ACD(F), probably due to the muscle dissection needed to obtain adequate surgical exposure.[23] When carefully and properly executed, cervical spine surgery can be effective with an acceptable rate of complications.[22]

Minimal invasive treatment

To reduce the risks of surgery, new minimally invasive percutaneous techniques for vertebral disc diseases have been developed in the last three decades. These techniques aim at removing a small amount of the central nucleus pulposus to reduce the intradiscal pressure or chemical irritation on sensory nerves and hence alleviate the nociceptive pain component.[24,25] In general, these percutaneous techniques have many advantages over surgery: 1) protection of surrounding tissues, 2) no scar and 3) performance under local anaesthesia in an outpatient basis.[25] However, one main limitation is that only contained soft-disc herniations can be treated with these techniques.[25]

There are several percutaneous techniques, relying either on pure mechanical (automated percutaneous discectomy), chemical (alcohol, oxygen-ozone), or thermal (laser, radiofrequency) decompression.[25] However, little information is published about these techniques and most data come from observational studies with low-level quality of evidence which makes it difficult for the clinician to decide which treatment modality should be used.[24] Of these techniques, percutaneous cervical nucleoplasty (PCN) has become the most often applied therapeutic option for cervical disk decompression among interventional pain specialists.[25] PCN was developed by Arthro- Care Corporation in the United States and first performed in July of 2000.[17] PCN uses Coblation technology to remove a portion of nucleus tissue and to create small channels within the herniated disc. During ablation, bipolar radiofrequency energy with low temperature (typically 40–70°C) is applied to create a highly focused plasma field between the electrodes and the tissue. As a result of the voltage gradient, charged particles accelerate towards the tissue and break down organic molecular bonds within the herniated disc into element molecules and low molecular weight gases; oxygen, nitrogen, hydrogen, and carbon dioxide. These gases escape through the needle and leads to shrinkage of the tissue in the disc, hence leading to disc decompression with minimal damage to surrounding healthy tissue.[26-28]

Several studies have demonstrated that PCN is an effective and safe technique in the treatment of (contained) herniated discs in patients with CRP.[24,28-33] However, the majority of the studies have a nonrandomized design[28,33], and moreover, the few identified Randomized Controlled Trials (RCTs)[24,31] are in general of poor methodological quality. Furthermore, none of these RCTs have ever compared the efficacy of PCN to surgery. Although the primary outcomes of PCN are promising and the application is encouraged in well-selected cases, more and better-designed studies with validated outcomes are needed.[29] To filling this gap of knowledge, we performed a RCT comparing PCN to surgical treatment in patients with CRP due to single-level contained soft-disc herniation. In our opinion it would be a very important improvement for the patient, if the same benefits of surgery could be achieved with PCN, without the serious complications that can occur during and after surgery.

Outline thesis

The overall aim of the work presented in this thesis was to gain better insight into the efficacy and safety of PCN compared to other treatments in patients with CRP due to a disc herniation. This thesis can be divided into three parts.

Part I focuses on identifying, evaluating, and summarizing the results of (non) randomized studies and compares percutaneous cervical nucleoplasty (PCN) with other treatments for patients with CRP due to a disc herniation. **Chapter 2** presents a Cochrane protocol in which we described, in detail, the process of conducting and maintaining a Cochrane systematic review on the effects of PCN in comparison with other treatments for patients with CRP due to a disc herniation. **Chapter 3** describes the results of our Cochrane systematic review to determine whether PCN improves clinical and functional outcomes compared to other treatments in patients with CRP due to a disc herniation.

In part II of this thesis, we focus on clearly describing the intervention techniques of our RCT because both of these techniques (PCN and ACD) are widely used in different ways. We also investigated Dutch neurosurgeons' treatment preferences for the management of a symptomatic disc herniation. To fulfil this part of the thesis we described in **Chapter 4** the operative technique of PCN and in **Chapter 5** the operative technique of ACD in a step-by-step manner with an accompanying video. In **Chapter 6** we present the results of a survey on the management of symptomatic cervical disc herniation among Dutch Neurosurgeons.

Part III of this thesis focusses on the results of our trial and the long-term effects of PCN in patients with CRP due to a disc herniation.

Chapter 7 presents the results of an RCT in which we compare the effects of PCN and ACD on a group of patients with CRP caused by a single-level contained soft-disc herniation.

Chapter 8 report the results of a retrospective cohort study which presents the long-term clinical results of percutaneous cervical nucleoplasty on patients with CRP due to a disc herniation.

Chapter 9 discusses the main findings of this thesis, addresses the study limitations, and considers various implications for daily practice and future research.

Chapter 10 gives an overall summary of the work.

References

1. Daffner SD, Hilibrand AS, Hanscom BS, Brislin BT, Vaccaro AR, Albert TJ. Impact of neck and arm pain on overall health status. Spine (Phila Pa 1976) 2003;28(17):2030-5.
2. Manchikanti L, Hirsch JA. Clinical management of radicular pain. Expert Rev Neurother 2015;15(6):681-93.
3. Thoomes EJ, Scholten-Peeters GGM, de Boer AJ, et al. Lack of uniform diagnostic criteria for cervical radiculopathy in conservative intervention studies: a systematic review. European Spine Journal 2012;21(8):1459-1470. DOI: 10.1007/s00586-012-2297-9.
4. Van Zundert J, Huntoon M, Patijn J, et al. 4. Cervical radicular pain. Pain Pract 2010;10(1):1-17.
5. Thoomes EJ, van Geest S, van der Windt DA, et al. Value of physical tests in diagnosing cervical radiculopathy: a systematic review. Spine J 2018;18(1):179-189.
6. Salemi G, Savettieri G, Meneghini F, et al. Prevalence of cervical spondylotic radiculopathy: a door-to-door survey in a Sicilian municipality. Acta Neurol Scand 1996;93(2-3):184-8.
7. Radhakrishnan K, Litchy WJ, O'Fallon WM, Kurland LT. Epidemiology of cervical radiculopathy. A population-based study from Rochester, Minnesota, 1976 through 1990. Brain 1994;117 (Pt 2):325-35.
8. Schoenfeld AJ, George AA, Bader JO, Caram PM, Jr. Incidence and epidemiology of cervical radiculopathy in the United States military: 2000 to 2009. J Spinal Disord Tech 2012;25(1):17-22.
9. Van Boxem K, Huntoon M, Van Zundert J, Patijn J, van Kleef M, Joosten EA. Pulsed radiofrequency: a review of the basic science as applied to the pathophysiology of radicular pain: a call for clinical translation. Reg Anesth Pain Med 2014;39(2):149-59.
10. Dower A, Davies MA, Ghahreman A. Pathologic Basis of Lumbar Radicular Pain. World Neurosurg 2019;128:114-121.
11. Thoomes EJ. Effectiveness of manual therapy for cervical radiculopathy, a review. Chiropr Man Therap 2016;24:45.
12. Thoomes EJ, Scholten-Peeters W, Koes B, Falla D, Verhagen AP. The effectiveness of conservative treatment for patients with cervical radiculopathy: a systematic review. Clin J Pain 2013;29(12):1073-86.
13. Cheng CH, Tsai LC, Chung HC, et al. Exercise training for non-operative and post-operative patient with cervical radiculopathy: a literature review. J Phys Ther Sci 2015;27(9):3011-8.
14. Conger A, Cushman DM, Speckman RA, Burnham T, Teramoto M, McCormick ZL. The Effectiveness of Fluoroscopically Guided Cervical Transforaminal Epidural Steroid Injection for the Treatment of Radicular Pain; a Systematic Review and Meta-analysis. Pain Med 2020;21(1):41-54.
15. Sleijser-Koehorst MLS, Coppieters MW, Heymans MW, Rooker S, Verhagen AP, Scholten-Peeters GGM. Clinical course and prognostic models for the conservative management of cervical radiculopathy: a prospective cohort study. Eur Spine J 2018;27(11):2710-2719.
16. Wong JJ, Côté P, Quesnele JJ, Stern PJ, Mior SA. The course and prognostic factors of symptomatic cervical disc herniation with radiculopathy: a systematic review of the literature. Spine J 2014;14(8):1781-9.
17. Sim SE, Ko ES, Kim DK, Kim HK, Kim YC, Shin HY. The results of cervical nucleoplasty in patients with cervical disc disorder: a retrospective clinical study of 22 patients. Korean J Pain 2011;24(1):36-43.
18. Liu WJ, Hu L, Chou PH, Wang JW, Kan WS. Comparison of Anterior Cervical Discectomy and Fusion versus Posterior Cervical Foraminotomy in the Treatment of Cervical Radiculopathy: A Systematic Review. Orthop Surg 2016;8(4):425-431.
19. Selvanathan SK, Beagrie C, Thomson S, et al. Anterior cervical discectomy and fusion versus posterior cervical foraminotomy in the treatment of brachialgia: the Leeds spinal unit experience (2008-2013). Acta Neurochir (Wien) 2015;157(9):1595-600.

20. Radcliff K, Zigler J, Zigler J. Costs of cervical disc replacement versus anterior cervical discectomy and fusion for treatment of single-level cervical disc disease: an analysis of the Blue Health Intelligence database for acute and long-term costs and complications. Spine (Phila Pa 1976) 2015;40(8):521-9.
21. Vleggeert-Lankamp CLA, Janssen TMH, van Zwet E, et al. The NECK trial: Effectiveness of anterior cervical discectomy with or without interbody fusion and arthroplasty in the treatment of cervical disc herniation; a double-blinded randomised controlled trial. Spine J 2018.
22. Hemmer C. Surgical Complications Associated With Cervical Spine Surgery. Orthop Nurs 2018;37(6):348-354.
23. Choi G, Lee SH, Bhanot A, Chae YS, Jung B, Lee S. Modified transcorporeal anterior cervical microforaminotomy for cervical radiculopathy: a technical note and early results. Eur Spine J 2007;16(9):1387-93.
24. Halim W, van der Weegen W, Lim T, Wullems JA, Vissers KC. Percutaneous Cervical Nucleoplasty vs. Pulsed Radio Frequency of the Dorsal Root Ganglion in Patients with Contained Cervical Disk Herniation; A Prospective, Randomized Controlled Trial. Pain Practice 2017;17(6):729-737. DOI: 10.1111/papr.12517.
25. Gangi A, Tsoumakidou G, Buy X, Cabral JF, Garnon J. Percutaneous techniques for cervical pain of discal origin. Semin Musculoskelet Radiol 2011;15(2):172-80.
26. Li J, Yan DL, Zhang ZH. Percutaneous cervical nucleoplasty in the treatment of cervical disc herniation. Eur Spine J 2008;17(12):1664-9.
27. Gerges FJ, Lipsitz SR, Nedeljkovic SS. A systematic review on the effectiveness of the Nucleoplasty procedure for discogenic pain. Pain Physician 2010;13(2):117-32.
28. Birnbaum K. Percutaneous cervical disc decompression. Surg Radiol Anat 2009;31(5):379-87.
29. Wullems JA, Halim W, van der Weegen W. Current evidence of percutaneous nucleoplasty for the cervical herniated disk: a systematic review. Pain Pract 2014;14(6):559-69.
30. Halim W, Wullems JA, Lim T, et al. The long-term efficacy and safety of percutaneous cervical nucleoplasty in patients with a contained herniated disk. Pain Pract 2013;13(5):364-71.
31. Cesaroni A, Nardi PV. Plasma disc decompression for contained cervical disc herniation: a randomized, controlled trial. Eur Spine J 2010;19(3):477-86.
32. de Rooij JD, Gadjradj PS, Soria van Hoeve JS, Huygen FJ, Aukes HA, Harhangi BS. Percutaneous Nucleoplasty for the Treatment of a Contained Cervical Disk Herniation. Clin Spine Surg 2017;30(9):389-391.
33. Nardi PV, Cabezas D, Cesaroni A. Percutaneous cervical nucleoplasty using coblation technology. Clinical results in fifty consecutive cases. Acta Neurochir Suppl 2005;92:73-8.

Part one

Management of cervical radicular pain due to a disc herniation

Chapter two

NUCLEOPLASTY FOR CERVICAL RADICULAR PAIN OR CERVICAL RADICULOPATHY, OR BOTH DUE TO A DISC HERNIATION: A PROTOCOL

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Cochrane Database of Systematic Reviews 2015, Issue 9. Art. No.: CD011852.

Abstract

This is a protocol for a Cochrane Review (Intervention). The Objectives are as follows: To determine whether nucleoplasty improves clinical and functional outcomes compared to surgery or conservative treatment for patients with cervical radicular pain, radiculopathy due to a disc herniation or both.

Background

Cervical radiculopathy (CR) is a common diagnosis with various treatment options available. In neurologically stable patients, various forms of conservative treatment are prescribed, such as rest, analgesics and non-steroidal anti-inflammatory drugs, physiotherapy, a cervical collar, or a combination of these. Conservative treatment leads to a spontaneous reduction of pain and disability in 40% of the patients (Lees 1963; Dillin 1986). One study evaluated the effects of conservative treatment for cervical radicular syndrome, and concluded that in the early phase of this disease a semi-hard cervical collar and rest or physiotherapy reduced neck and arm pain, compared to a 'wait and see' policy (Kuijper 2009).

When conservative treatment fails and symptoms persist or increase in severity, surgical treatment is considered (Nardi 2005). The goals of surgery are to alleviate pressure on the affected cervical spinal nerve and the roots of the nerve, and if necessary to restore vertebral alignment and spine stabilization. The affected disc will be removed during the surgical procedure, with or without fusing of the two adjacent vertebral bodies. Bone grafts can be used to stimulate the fusion process (Jacobs 2012). This surgical technique has been widely accepted as the standard treatment for CR for more than five decades. However, this procedure is associated with a small risk of serious complications such as perforation of the oesophagus, injuries to the carotid or vertebra and severe neurological complications. The results of surgery are not always satisfactory and the overall outcome may be similar to conservative treatment (Nikolaidis 2010; Gebremariam2012; van Middelkoop 2013). Currently, there is an evolving trend in all spinal surgery toward less invasive techniques. Nucleoplasty is such a minimally invasive technique, and is a treatment which uses radiofrequency technology for percutaneous disc decompression.

Description of the condition

There is no universally accepted definition of CR (Thoomes 2012). It is defined by Carette and Fehlings as a neurologic condition characterised by dysfunction of a cervical spinal nerve, the roots of the nerve, or both. It usually presents with pain in the neck and one arm, with a combination of sensory loss, loss of motor function, or reflex changes in the affected nerve-root distribution (Carette 2005). Some authors indicate that cervical radicular pain must be distinguished from CR (Van Zundert 2010) . In CR there is a clear loss of sensory and/or motor function, while radicular pain is characterised by the formation of ectopic pulses. These two disorders can also coexist and may be caused by the same anatomical changes such as intervertebral disc herniation, radiculitis due to arthritis, narrowing of the intervertebral foramen, infection, or inflammatory exudates. Radicular pain can deteriorate into CR due to disease progression (Van Zundert 2010).

The epidemiological data on CR are minimal. In a retrospective population-based study from Rochester, Minnesota in the United States (1976 to 1990) the annual incidence of CR was 83 per 100,000 people. The annual incidence rate was 107.3 per 100,000 for men and 63.5 per 100,000 for women (Radhakrishnan 1994). A door-to-door survey in a Sicilian municipality reported a prevalence of 3.5 per 1000 person-years (Salemi 1996). Both studies found an association between age and the development of CR, with a peak incidence in the sixth decade of life for people of both genders (Radhakrishnan 1994 ; Salemi 1996). In an epidemiological review of a population of American soldiers (2000 to 2009) the incidence of CR was 1.79 per 1000 person-years. The incidence was calculated from a prospectively-collected military database, which includes more than 20,000 cases of CR from an ethnically- and socio-economically diverse cohort. The annual incidence rate was 1.76 per 1000 person-years for men and 1.95 per 1000 person-years for women (Schoenfeld 2012). Age is an important risk factor for developing CR (Radhakrishnan 1994; Salemi 1996; Schoenfeld 2012) and that females have a greater risk of developing CR than males (Schoenfeld 2012).

Description of the intervention

In 2000, the United States of America's Food and Drug Administration approved nucleoplasty as a treatment for contained disc herniations (Gerges 2010). Nucleoplasty is a minimally invasive technique, which uses coagulation and tissue ablation for percutaneous disc decompression. Radiofrequency energy is applied to a conductive medium (a one mm diameter bipolar instrument) and forms a highly focused plasma field around the energised electrodes. This plasma field contains highly ionised particles, which break organic molecular bonds and form small channels within the nucleus pulposus tissue, resulting in decompression of the herniated disc. By-products such as low-molecular-weight inert gases and elementary molecules are removed via the needle (Chen 2003). The removal of disc tissue is a non-heat-driven process and is associated with temperatures of between 40 ℃ to 70 ℃. In this way the integrity of the surrounding healthy tissue is preserved. Approximately one mL of disc tissue volume is removed, which corresponds with a reduction of the discal volume by 10% to 20% (Gerges 2010). One study examined the effect of nucleoplasty on the tissue and its authors concluded that volumetric removal of the nucleus pulposus tissue can be performed without disruption or necrosis of non-targeted nucleus, annulus, endplate, nerve root or spinal cord (Chen 2003). This is supposed to down-regulate local inflammatory mediators, reduce disc size, and stimulate the healing process (Chen 2003).

How the intervention might work

The primary goal of nucleoplasty is volumetric reduction of the tissue of the nucleus pulposus, which is vaporised at lower temperatures and causes a decrease in

intradiscal pressure of the herniated disc. Several studies have demonstrated that cervical nucleoplasty is a safe and effective technique (Gerszten 2006; Birnbaum 2009; Sim 2011; Halim 2013). A recent observational study showed that complete or partial long-term pain relief can be safely achieved using nucleoplasty in patients with a contained cervical herniated disk (Halim 2013). In the vast majority of these patients, nucleoplasty achieves a long-term reduction in pain, good clinical outcomes, reduced pain medication use, and higher patient satisfaction (Halim 2013).

Careful selection of patients is important for successful nucleoplasty (Gerges 2010 ; Halim 2013). Patients with incomplete annular tears and minimally degenerated discs may benefit the most (Gerges 2010; Halim 2013). Compared to surgical treatment, nucleoplasty is a minimally invasive percutaneous technique performed on an outpatient basis with a fast recovery time. There have been no neurological complications reported from the procedure itself, although this claim is subject to publication bias. Until now, very limited evidence has been found on the effects of nucleoplasty in patients with CR.

Why is it so important to do this review

When the severe symptoms of patients with CR do not improve with conservative treatment, surgical treatment is considered. Surgery comes with risks, reoperation rates are significant (Veeravagu 2014) and freedom from pain is not guaranteed. Long-term pain medication and other forms of conservative treatment carry their own risks and costs. We would consider it an important improvement for the patient, if the same benefits of surgery could be achieved with nucleoplasty, without serious complications and at reduced cost. At present, there is only one systematic review available focusing on nucleoplasty treatment options for people with CR (Wullems 2014), which did not use the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach (Guyatt 2011) to measure the quality of evidence. The Wullems review measures the risk of bias of the randomised clinical trials (RCTs) using the method described by Furlan 2009 and the non-RCTs using the Newcastle Ottawa Scale (NOS), despite the fact that the NOS is designed for prospective cohort studies. In contrast to Wullems 2014, we will use the GRADE approach to assess the quality of the body of evidence and we will use the Cochrane 'Risk of bias' tool (Higgins 2011) and items from the Downs and Black checklist (Downs 1998) to measure the risk of bias. We will also measure psycho-social outcomes as secondary outcomes.

Objectives

To determine whether nucleoplasty improves clinical and functional outcomes compared to surgery or conservative treatment for patients with cervical radicular pain, radiculopathy due to a disc herniation or both.

Methods

Criteria for considering studies for this review

Types of studies

We will include full journal publications of quantitative studies, namely randomised controlled trials (RCTs), quasi-randomised controlled trials (using a method of allocating people to a treatment that is not strictly random, e.g. by date of birth, alternation) and non-randomised controlled trials (NRCTs) because of the limited number of RCTs. We will exclude letters, editorials, commentaries, conference proceedings, meeting abstracts, lectures and addresses, narrative reviews, and qualitative research.

Types of participants

We will include studies involving male or female patients (18 years of age or older), with cervical radicular pain, radiculopathy, or both, due to a single level degenerative disc disease of the cervical spine corresponding to the affected level. We will include degenerative disc diseases such as a narrowing of the intervertebral foramen, intervertebral disc herniations and radiculitis due to the degenerative effect of arthritis. The duration of symptoms must be at least six weeks, with insufficient relief of symptoms with conservative treatment. We will exclude studies involving patients with previous surgery of the cervical spine, inflammatory spinal arthritis and malignancy of the cervical spine region.

Types of interventions

We will include studies with nucleoplasty as the index treatment. The index treatment will be compared to the following:

- no treatment or placebo treatment;
- conservative treatment (such as oral medication (e.g. non-steroidal anti-inflammatory drugs, muscle relaxants), physiotherapy, manual therapy, spinal modulation, bed rest, cervical collar or traction);
- surgery (anterior and posterior decompression, either with non-fusion techniques; fusion techniques by plate, cage, autograft, allograft material, or artificial disc; or a combination).

Types of outcome measures

We will collect all outcome data at short-term follow-up (up to and including 3 months), medium-term follow-up (more than 3 and less than 12 months) and long-term follow-up (1 year or longer).

Primary outcomes

- Pain intensity of the arm and neck expressed on a visual analogue scale or other measure of pain scale (e.g. visual analogue scale for pain (Sriwatanakul 1983), ordinal scale (Von Korff 2000)).
- Neck-related functional status, expressed on a neck-specific scale (e.g. Neck Disability Index (Vernon 2008)).
- Recovery measured by global perceived effect (e.g. proportion of patients recovered, subjective improvement of symptoms).

Secondary outcomes

- Global health status (e.g. The Short Form (36) Health Survey (Ware 1992), EuroQoL 5 Dimension (Williams 1990), Sickness Impact Profile (de Bruin 1994)).
- Work-related disability (rate of health-related absenteeism or unemployment).
- Psycho-social outcomes (e.g. anxiety, depression, pain behaviour).
- Adverse effects (totality of possible adverse consequences of an intervention or therapy such as early adverse events anddelayed complications).

Search methods for identification of studies

Electronic searches

The search will be conducted from inception to the present in the following databases:

- EMBASE (Excerpta Medica Database, Elsevier)
- MEDLINE (Medical Literature Analysis and Retrieval System Online, OvidSP)
- CENTRAL (Cochrane CENTRAL Register of Controlled Trials, The Cochrane Library)
- Web of Science (Thomson Reuters)
- Scopus (Elsevier)
- CINAHL (Cumulative Index to Nursing and Allied Health Literature, EBSCO
- PubMed
- ClinicalTrials.gov
- Google Scholar
- PEDro (Physiotherapy Evidence Database)
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP)

We will apply no language restrictions. We will not use an RCT filter in MEDLINE or EMBASE, as the set of intervention terms will limit the results sufficiently. The searches will be conducted by an experienced librarian at the Erasmus Medical Center Rotterdam. We will contact the Trials Search Coordinator of the Cochrane Back Review Group (CBRG) to search the group's Trials Register through the Cochrane Register of Studies (CRS) for studies not in CENTRAL. The MEDLINE strategy is given in Appendix 1.

Searching other resources

We will search the System for Information on Grey Literature (SIGLE) database through OpenSigle, subheading biological and medical sciences, to search for trials that might have been missed by other sources. We will also consult personal files, screen references, and communicate with the CBRG and content experts in order to identify additional studies.

DATA COLLECTION AND ANALYSIS

Selection of studies

Two authors (JDdR and BSH) will screen the titles and abstracts of all studies retrieved by the searches to identify those meeting the inclusion criteria. The authors will select the studies independently and discuss the results to make the final selection. They will make the final decision after reading the full text of all potentially eligible articles. In case of disagreement, they will consult with a third author (JGG). We will retrieve publications in all languages and seek appropriate translation if necessary. Study flow diagrams, following the template described in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Liberati 2009), will be used to illustrate the results of the search and the process of screening and selecting studies for inclusion in the review.

Data extraction and management

Two authors (JDdR and BSH) will independently extract the data from each included trial using a standard form. These authors will also pilot test the standardised form on a sample of three articles not included in the review. The authors will examine inter-rater reliability. The following data will be extracted from each study: study design, characteristics of the study population (e.g. number of participants, age, gender, nature and duration of the health problem, inclusion and exclusion criteria), study characteristics (e.g. country, recruitment modality, setting and company sponsorship, risk of bias), description of the experimental and control interventions, co-interventions, duration of follow-up, outcomes assessed, and results. The two authors will discuss any disagreement and consult a third review author if necessary.

Assessment of risk of bias in included studies

Two review authors (JDdR and BSH) will independently assess the risks of bias of all included studies. In case of disagreement, they will consult a third author (APV). We will attempt to obtain additional information from authors of the studies regarding any items that remain unclear. The risk of bias for both RCTs and NRCTs will be assessed using the criteria recommended by the CBRG (Furlan 2009; Higgins 2011), together with items from the Downs & Black checklist (Downs 1998) (Appendix 2).

We will examine all trials for five types of bias categories: selection bias, performance bias, attrition bias, measurement/detection biasand selective reporting. The 'Assessment of risk of bias' form will be piloted and tested for intra-observer and inter-observer reliability. The 'Risk of bias' criteria will be scored as high, low or unclear risk, and will be reported in the 'Risk of bias' table. The additional details on quality assessment for each outcome are described in the Data synthesis section.

Measures of treatment effect

Dichotomous outcomes will be analysed by calculating the relative risk (RR). Continuous outcomes (e.g. visual analog scale, numeric rating scale) will be analysed by calculating the mean difference (MD) when the same instrument is used to measure outcomes, or the standardised mean difference (SMD) when different instruments are used to measure outcomes. The uncertainty will be expressed with 95% confidence intervals (95% CI). For each treatment comparison, we will calculate an effect size and a 95% CI and display them as forest plots.

Unit of analysis issues

We do not expect to identify unit of analysis issues with regard to cross-over or cluster randomised trials. However, we do expect to find repeated observations on participants in most of the eligible trials. In this case we will follow the suggested strategy of defining the outcomes (already stated above) as well as the time points a priori (Higgins 2011). The time points are short (less than 3 months after randomisation), intermediate (at least 3 months but less than 12 months after randomisation) and long term (12 months or more after randomisation). When there are multiple time points that fall within the same category, the time points that are closest to the end of the treatment, and to 6 months and 12 months will be used. If studies include multiple treatment arms and, therefore, multiple comparisons, we will aim to select the most appropriate comparison. If two groups are considered to be the same (e.g. 2 controls: waiting list and no treatment) the 'shared' intervention will be split in order to include two (reasonably independent) comparisons.

Dealing with missing data

We will contact the trial authors to request missing data. When standard deviations (SDs) are not reported and cannot be acquired from the trial authors we will use one of the following three options; calculation of the missing SDs from other reported data (e.g. mean differences, P values, number of observations); if graphs with error bars are available we will measure them manually and impute by taking the SD of similar sized studies for that outcome. Finally, if no measure of variation is reported in the text, we will estimate the SD based upon other studies with a similar population and risk of bias.

Assessment of heterogeneity

We will assess clinical heterogeneity based on information on study population, interventions, control interventions and outcomes. Additionally, we will assess methodological heterogeneity by examining the variability in study design (RCT versus NRCTs) and risk of bias. We will assess statistical heterogeneity between trials using the values of I^2 that are greater than 75% showing a very high level of heterogeneity, in which case, we will not pool studies. In all other cases we will pool studies using a random-effects model.

Assessment of reporting biases

We will create and use funnel plots to assess publication bias.

Data synthesis

Our approach to evidence synthesis will be adapted from the Cochrane Collaboration Methods for randomised trials and from other reviews of non-randomised studies. For risks, we will capture or calculate the incidence and/or prevalence for the population included in each study. We will group the analyses separately according to the control interventions, the outcomes measured, and the timing of outcome assessment. The outcome measures from the individual trials will be combined through meta-analysis where possible (clinical comparability of population, intervention and outcomes between trials) using a random-effects model. If a meta-analysis is not possible, the results from clinically comparable trials will be described qualitatively in the text.

Regardless of whether there are sufficient data available to use quantitative analyses to summarise the data, we will assess the overall quality of the evidence for each outcome. To accomplish this, we will use the GRADE approach, as recommended in the Cochrane Handbook (Higgins 2011) and adapted in the updated CBRG method guidelines (Furlan 2009).

Following GRADE guidelines, the final grade for quality of evidence for each sub-question will be categorised as: high, moderate, low, or very low. The evidence available to answer each subquestion will be graded on the following domains: study design, risk of bias, inconsistency, indirectness, imprecision, publication bias, magnitude of effect, dose-response gradient and influence of all plausible residual confounding. These domains are further discussed in Appendix 3 of this protocol. The judgment of these factors will be determined by two review authors (JdR and APV). Single randomised studies will be considered inconsistent, imprecise if $N < 300$ for dichotomous outcomes and < 400 for continuous outcomes and in that case will provide 'low quality evidence'. This can be further downgraded to 'very low quality evidence' if there are also limitations in design (i.e. high risk of bias), indirectness or other considerations. We will use RevMan software (RevMan 2014) to analyse the data.

'Summary of findings' tables

We will include the essential outcomes and the timing of outcome assessment of pain intensity, neck-related functional status, recovery, global health status, work disability, psycho-social outcomes and adverse effects. We will report these outcomes in terms of the three different comparisons listed at Types of interventions.

Subgroup analysis and investigation of heterogeneity

We will perform subgroup analyses for RCTs versus CCTs. If data allow, we will perform subgroup analysis to investigate the effects of different control groups, different degenerative disc diseases, location of the health problem (neck versus arm) and the duration of the problem (chronic versus (sub(acute)).

Sensitivity analysis

We will perform a sensitivity analysis to assess the influence of including trials at high risk of bias. We define a trial meeting fewer than five criteria in the 'Risk of bias' analysis as being at high risk of bias. We will also perform a second sensitivity analysis to investigate the influence of high levels of attrition (15% or more participants lost to follow up).

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We thank Wichor Bramer, Biomedical Information Specialist, from the Medical Library of the Erasmus University Medical Center for developing the search strategies used to consult the Cochrane Central Register of Controlled Trials, MEDLINE and EMBASE.

Contribution of authors

JDdR designed the protocol. JDdR drafted the protocol with help from the other authors. All authors read and approved the final version.

Declaration of interest

None known.

REFERENCES

Birnbaum K. Percutaneous cervical disc decompression. Surgical and Radiologic Anatomy: SRA 2009;31(5):379-87.

Carette S, Fehlings MG. Clinical practice. Cervical radiculopathy. New England Journal of Medicine 2005;353(4):392-9.

Chen YC, Lee SH, Chen D. Intradiscal pressure study of percutaneous disc decompression with nucleoplasty in human cadavers. Spine (Phila Pa 1976) 2003;28(7):661-5.

de Bruin AF, Diederiks JP, de Witte LP, Stevens FC, Philipsen H. The development of a short generic version of the Sickness Impact Profile. Journal of Clinical Epidemiology1994;47(4):407-18.

Dillin W, Booth R, Cuckler J, Balderston R, Simeone F, Rothman R. Cervical radiculopathy. A review. Spine(Philadelphia, Pa. : 1986) 1986;11(10):988-91.

Downs S, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomized and non-randomised studies of health care interventions. Journal of Epidemiology and Community Health 1998;52:377-84.

Furlan AD, Pennick V, Bombardier C, van Tulder M. 2009 updated method guidelines for systematic reviews in the Cochrane Back Review Group. Spine 2009;34(18):1929-41.

Gebremariam L, Koes BW, Peul WC, Huisstede BM. Evaluation of treatment effectiveness for the herniated cervical disc: a systematic review. Spine (Phila Pa 1976) 2012;37(2):E109-18.

Gerges FJ, Lipsitz SR, Nedeljkovic SS. A systematic review on the effectiveness of the Nucleoplasty procedure for discogenic pain. Pain Physician 2010;13(2):117-32.

Gerszten PC, Welch WC, King JT Jr. Quality of life assessment in patients undergoing nucleoplasty-based percutaneous discectomy. Journal of Neurosurgery. Spine 2006;4(1):36-42.

Gordon H. Guyatt, Andrew D. Oxman, Victor Montori,Gunn Vist, Regina Kunz, Jan Brozek, Pablo Alonso-Coello,Ben Djulbegovic, David Atkins, Yngve Falck-Ytter, JohnW. Williams Jr, Joerg Meerpohl, Susan L. Norris, Elie A. Akl, Holger J. Schünemann. GRADE guidelines: 5. Rating the qualityof evidence—publication bias. Journal of Clinical Epidemiology December 2011;64(12):1277-1282.

Halim W, Wullems JA, Lim T, Aukes HA, van der Weegen W, Vissers KC, et al. The long-term efficacy and safety of percutaneous cervical nucleoplasty in patients with a contained herniated disk. Pain Practice 2013;13(5):364-71.

Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available fromwww.cochrane-handbook.org.

Jacobs WC, Arts MP, van Tulder MW, Rubinstein SM, van Middelkoop M, Ostelo RW, et al. Surgical techniques for sciatica due to herniated disc, a systematic review. European Spine Journal 2012;21(11):2232-51.

Kuijper B, Tans JT, Beelen A, Nollet F, de Visser M. Cervical collar or physiotherapy versus wait and see policy for recent onset cervical radiculopathy: randomised trial. BMJ Oct 72009;339:b3883.

Lees F, Turner JW. Natural history and prognosis of cervical spondylosis. British Medical Journal Dec 281963;2(5373):1607-10.

Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J, Moher D. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration.. British Medical Journal 2009 Jul21;339:b2700. doi: 10.1136/bmj.b2700.

Mueller PS, Montori VM, Bassler D, Koenig BA, Guyatt GH. Ethical issues in stopping randomized trials early because of apparent benefit. Ideas and Opinions 2007;146:878-82.

Nardi PV, Cabezas D, Cesaroni A. Percutaneous cervical nucleoplasty using coblation technology. Clinical results in fifty consecutive cases. Acta Neurochirurgica Supplement2005;92:73-8.

Nikolaidis I, Fouyas IP, Sandercock PA, Statham PF. Surgeryfor cervical radiculopathy or myelopathy. Cochrane Database of Systematic Reviews 2010, Issue 1. [DOI:10.1002/14651858.CD001466.pub3]

Radhakrishnan K, Litchy WJ, O'Fallon WM, Kurland LT .Epidemiology of cervical radiculopathy. A population-based study from Rochester, Minnesota, 1976 through 1990. Brain1994;117(Pt 2):325-35.

The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Salemi G, Savettieri G, Meneghini F, Di Benedetto ME,Ragonese P, Morgante L, et al. Prevalence of cervical spondylotic radiculopathy: a door-to-door survey in a Sicilian municipality. Acta Neurologica Scandinavica 1996;93(2-3):184-8.

Schoenfeld AJ, George AA, Bader JO, Caram PM Jr. Incidenc eand epidemiology of cervical radiculopathy in the United States military: 2000 to 2009. Journal of Spinal Disorders & Techniques 2012;25(1):17-22.

Sim SE, Ko ES, Kim DK, Kim HK, Kim YC, Shin HY. The results of cervical nucleoplasty in patients with cervical disc disorder: a retrospective clinical study of 22 patients. Korean Journal of Pain 2011;24(1):36-43.

Sriwatanakul K, Kelvie W, Lasagna L, Calimlim JF, Weis OF, Mehta G. Studies with different types of visual analog scales for measurement of pain. Clinical Pharmacology Therapeutics1983;34(2):234-9.

Thoomes EJ, Scholten-Peeters GG, de Boer AJ, Olsthoorn RA, Verkerk K, Lin C, et al. Lack of uniform diagnostic criteria for

cervical radiculopathy in conservative intervention studies: a systematic review. European Spine Journal 2012;21(8):1459-70.

van Middelkoop M, Rubinstein SM, Ostelo R, van Tulder MW, Peul W, Koes BW, et al. Surgery versus conservative care for neck pain: a systematic review. European Spine Journal2013;22(1):87-95.

Van Zundert J, Huntoon M, Patijn J, Lataster A, Mekhail N, van Kleef M. 4. Cervical radicular pain. Pain Practice2010;10(1):1-17.

Veeravagu A, Cole T, Jiang B, Ratliff JK. Revision rates andc omplication incidence in single- and multilevel anterior cervical discectomy and fusion procedures: an administrative database study. Spine Journal 2014;14(7):1125-3.

Vernon H. The Neck Disability Index: state-of-the-art, 1991-2008.Journal of Manipulative and Physiological Therapeutics2008;31(7):491-502.

Von Korff M, Jensen MP, Karoly P. Assessing global pain severity by self-report in clinical and health services research. Spine(Phila Pa 1976) 2000 Dec 5;15;25(24);:3140-51.

Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Medical Care 1992;30(6):473-83.

Williams A. EuroQol--a new facility for the measurement of health-related quality of life. The EuroQol Group. Health Policy1990;16(3):199-208.

Wullems JA, Halim W, van der Weegen W. Current evidence of percutaneous nucleoplasty for the cervical herniated disk: a systematic review. Pain Practice 2014;14(6):559-69. [DOI:10.1111/papr.12122]

APPENDICES

Appendix 1.

MEDLINE strategy (((neck/ OR Neck Muscles/ OR exp Cervical Vertebrae/ OR neck pain/ OR exp arm/ OR exp shoulder/ OR Shoulder Pain/ OR Shoulder Joint/ OR (neck OR arm OR (upper ADJ3 (extremit* OR limb*)) OR shoulder* OR cervic* OR cervix* OR c1 OR c2 OR c3 OR c4 OR c5 OR c6 OR c7)) AND (radiculopathy/ OR Polyradiculoneuropathy/ OR spinal cord compression/ OR exp Spinal Nerve Roots/ OR Intervertebral Disc Displacement/ OR (radiculalg* OR radiculopath* OR polyradiculopath* OR Polyradiculoneuropath* OR (Compress* ADJ3 Myelopath*) OR radiculitis OR ((radicul* OR nerve root OR nerve roots) ADJ3 (pain* OR neuralg*)) OR ((Spinal OR nerve OR ventral OR dorsal) ADJ3 (Root* OR cord*)) OR (vertebral ADJ3 compress*) OR ((disc OR discs OR discogen* OR disk OR disks OR vertebr* OR intervertebr*) ADJ6 (herni* OR pain* OR protrus* OR displace*))))) OR (Brachial Plexus Neuritis/ OR (((cervicobrach* OR cervico-brachial OR cervical brachial) ADJ3 neuralg*) OR ((arm neck shoulder OR neck shoulder arm OR shoulder arm neck OR cervical*) ADJ syndrom*) OR (cervicobrach* ADJ3 (disease* OR pain* OR syndrome*)) OR cervicobrachialg*))) AND ((((Plasma OR laser OR thermal OR needle OR percutan*) ADJ6 (decompression OR compression OR discectom* OR removal)) OR coblation OR Nucleoplast* OR pldd))

Appendix 2.

Criteria for assessing risk of bias for internal validity for randomised and non-randomised studies (Downs 1998; Furlan 2009)

Selection bias

Random sequence generation

Risk of selection bias is low if the investigators describe a random component in the sequence generation process, such as referring to a random number table, using a computer random number generator, coin tossing, shuffling cards or envelopes, throwing dice, drawing lots, or minimising (minimisation may be implemented without a random element, and this is considered to be equivalent to being random).

Risk of selection bias is high if the investigators describe a non-random component in the sequence generation process, such as sequence generated by odd or even date of birth, date (or day) of admission, hospital or clinic record number or allocation by judgement of the clinician, preference of the participant, results of a laboratory test or a series of tests or availability of the intervention. If it is a non-randomised study, this will be rated as high risk of bias.

Allocation concealment
Risk of selection bias is low if participants and investigators enrolling participants could not foresee assignment because one of the following, or an equivalent method, was used to conceal allocation: central allocation (including telephone, web-based and pharmacy controlled randomisation); sequentially numbered drug containers of identical appearance; or sequentially numbered, opaque, sealed envelopes.

Risk of bias is high if participants or investigators enrolling participants could possibly foresee assignments and thus introduce selection bias, such as allocation based on using an open random allocation schedule (e.g. a list of random numbers); assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or non-opaque or were not sequentially numbered); alternation or rotation; date of birth; case record number; or other explicitly unconcealed procedures.

If it is a non-randomised study, this will be rated as high bias.

Selection bias (population)*
Risk of selection bias is low if participants in different intervention groups were recruited from the same population.

Selection bias (timing)*
Risk of selection bias is low if participants in different intervention groups were recruited over the same time.

Adjustment for confounding*
Risk is low if no significant group differences were shown. Risk is high if the effect of the main confounders was not investigated or if no adjustment was made in the final analyses.

Appendix 3

The GRADE approach to evidence synthesis

The quality of evidence will be categorised as follows:

- High (●●●●): further research is very unlikely to change the confidence in the estimate of effect.
- Moderate (●●●○): further research is likely to have an important impact in the confidence in the estimate of effect.
- Low (●●○○): further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
- Very low (●○○○): any estimate of effect is very uncertain.

The evidence available to answer each sub-question will be graded on the domains in the following manner:

1. Study design
2. Risk of bias

Limitations in the study design and implementation may bias the estimates of the treatment effect. Our confidence in the estimate of the effect and in the following recommendation decreases if studies suffer from major limitations. We will examine all studies on five types of biases:

a) Selection (random sequence generation, allocation concealment, group similarities at baseline)
b) Performance (blinding of participants, blinding of healthcare providers)
c) Attrition (drop outs and intention-to-treat analysis)
d) Measurement (blinding of the outcome assessors and timing of outcome assessment)
e) Reporting bias (selective reporting)

3. Inconsistency

Inconsistency refers to an unexplained heterogeneity of results. Widely differing estimates of the treatment effect (i.e. heterogeneity or variability in results) across studies suggest true differences in underlying treatment effect. Inconsistency may arise from differences in: populations (e.g. drugs may have larger relative effects in sicker populations), interventions (e.g. larger effects with higher drug doses), or outcomes (e.g. diminishing treatment effect with time). The quality of evidence will be downgraded as follows:

- by one level: when the heterogeneity or variability in results is large (for example: I^2 above 80%)
- by two levels: when the heterogeneity or variability in results is large AND there was inconsistency arising from populations, interventions or outcomes.

4. Indirectness

Indirect population, intervention, comparator, or outcome - the question being addressed in this systematic review is different from the available evidence regarding the population, intervention, comparator, or an outcome in the included randomised trial. The quality of evidence will be downgraded as follows:

- by one level: when there is indirectness in only one area
- by two levels: when there is indirectness in two or more areas

5. Imprecision

Results are imprecise when studies include relatively few patients and few events and thus have wide confidence intervals around the estimate of the effect. In this case we judge the quality of the evidence lower than it otherwise would be because of consequent uncertainty in the results. Each outcome is considered separately.

For dichotomous outcomes

We will consider imprecision for either of the following two reasons:

a) There is only one study. When there is more than one study, the total number of events is less than 300 (a threshold rule-of-thumb value) (Mueller 2007).
b) 95% confidence interval around the pooled or best estimate of effect includes both i no effect and ii appreciable benefit or appreciable harm. The threshold for 'appreciable benefit' or 'appreciable harm' is a relative risk reduction (RRR) or relative risk increase (RRI) greater than 25%.The quality of the evidence will be downgraded as follows:

- by one level: when there is imprecision due to (a) or (b)
- by two levels: when there is imprecision due to (a) and (b)

For continuous outcomes

We will consider imprecision for either of the following two reasons:

a) There is only one study. When there is more than one study, total population size is less than 400 (a threshold rule-of-thumb value; using the usual α and β, and an effect size of 0.2 SD, representing a small effect).
b) 95% confidence interval includes no effect and the upper or lower confidence limit crosses an effect size (standardised mean difference)of 0.5 in either direction.

The quality of the evidence will be downgraded as follows:

- by one level: when there is imprecision due to (a) or (b)
- by two levels: when there is imprecision due to (a) and (b)

6. Publication bias

Publication bias is a systematic underestimate or overestimate of the underlying beneficial or harmful effect due to the selective publication of studies.

The quality of evidence will be downgraded as follows:

- by one level: when the funnel plot suggests publication bias

7. Magnitude of the effect
8. Dose response gradient
9. Influence of all plausible residual confounding

Chapter three

NUCLEOPLASTY FOR CERVICAL RADICULAR PAIN DUE TO A DISC HERNIATION: A SYSTEMATIC REVIEW

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Abstract

Background

Cervical Radicular Pain (CRP) due to a disc herniation is a common neurological condition and several treatment options are available. CRP usually presents with pain in the neck and one arm, with muscle weakness and/or numbness or tingling in fingers or hands. There is no universally accepted definition of CRP and epidemiological data on CRP are scarce.

When conservative treatment fails and symptoms persist or increase in severity, surgical treatment is considered. Surgery may come with risks and freedom from pain is not guaranteed. Long-term pain medication and other forms of conservative treatment also carry their own risks and costs. Recently, nucleoplasty, a new treatment for contained disc herniations was developed. Compared to surgery, nucleoplasty is a minimally invasive treatment which is performed on an outpatient basis with no neurological complications reported from the procedure itself.

Objectives

What is the effect of nucleoplasty on clinical and functional outcomes compared to conservative treatment, minimal invasive interventions and surgery in patients with CRP due to a disc herniation.

Search Methods

We searched in CENTRAL, MEDLINE, Embase, CINAHL, Web of Science, Scopus, PEDro, PubMed, ClinicalTrials.gov, World Health Organisation (WHO) International Clinical Trials Registry Platform (ICTRP), and Google Scholar from inception to October 5th, 2021. We also searched the SIGLE database, screened references of included studies, and communicated with the Cochrane Back and Neck group and content experts to identify additional studies.

Selection criteria

We included randomized controlled trials (RCTs) and non-randomized controlled trials (NRCTs) that investigated nucleoplasty compared to conservative treatment, minimally-invasive interventions or surgery for patients with CRP due to a disc herniation. The primary outcomes were pain intensity of the arm and neck, neck-related functional status and recovery. The secondary outcomes were global health status, work-related disability, psycho-social outcomes, and adverse effects.

Data collection and analyses

Two review authors independently screened the references, and we used the Cochrane's Risk-Of-Bias tool for RCTs and the Risk Of Bias In Non-randomized Studies-of Interventions (ROBINS-I) tool to assess the risk of bias of the included studies. We determined the certainty of evidence using the GRADE approach.

Main results

We included four RCTs (224 participants) and two NRCTs (129 participants) with patients with CRP due to a disc herniation. The risk of bias was high in all RCTs, and 'critical' in the two NRCTs, which were therefore excluded from the analyses.

Comparison 1 Nucleoplasty versus no treatment or placebo

We did not find any RCT or NRCT on this comparison.

Comparison 2 Nucleoplasty versus conservative treatment

One RCT evaluated nucleoplasty with conservative care. We found low-certainty of evidence that nucleoplasty may reduce pain intensity slightly (0-100 scale) at short-term follow-up (Mean Difference (MD) -22.71, 95% CI -30.10 to -15.32), low-certainty of evidence for little to no difference in pain intensity at medium-term follow-up (MD -15.96, 95% CI -23.15 to -8.77), and low-certainty of evidence that nucleoplasty may reduce pain intensity at long-term follow-up (clinically relevant MD -29.28, 95% CI -36.40 to -22.16).

We found low-certainty of evidence that nucleoplasty may result in no difference in neck-related functional status at short-term follow-up (0-50 scale) (MD -2.48, 95% CI -5.11 to 0.15), medium-term follow-up (MD -0.50, 95% CI -3.20 to 2.20) and long-term follow-up (MD -4.30, 95% CI -6.83 to -1.77).

Compared to conservative treatment, nucleoplasty may increase global health status - physical function at long-term follow-up (clinically relevant MD 5.37, 95% CI 1.30 to 9.44), but not at shorter term.

The evidence is uncertain about the risk of adverse effects between treatments.

This study did not report on work-related disability and psycho-social outcomes.

Comparison 3 Nucleoplasty versus pulsed radio frequency of the dorsal root ganglion

One RCT evaluated nucleoplasty versus pulsed radiofrequency. The certainty of the evidence for all outcomes was very low. At short-term follow-up nucleoplasty may result in no difference in pain intensity (0-100 scale) (MD -7.9, 95% CI-29.45 to 13.65), neck-related functional status (0-50 scale) (MD 0.30, 95% CI -6.97 to 7.57) and recovery (MD -5.10, 95% CI -29.92 to 19.72).

There is no difference in risk of adverse effects between groups at short-term follow-up (RR 1.0, 95% CI 0.17 to 5.83) (very low certainty).

This study did not report on global health status, work-related disability and psycho-social outcomes.

Comparison 4 Nucleoplasty versus discectomy

Two RCTs evaluated nucleoplasty versus surgery. We found very low to low-certainty of evidence that nucleoplasty may result in little to no difference in arm pain intensity (VAS: 0 mm-10 mm scale) at short-term (2 RCTs, no meta-analysis, MDs were -0.90 and 0.80), medium-term (1 RCT, MD 0.70, 95% CI 0.36 to 1.04; Analysis 3.1) and long-term follow up (1 RCT, MD 0.70, 95% CI -0.84 to 2.24).

We found low-certainty of evidence that nucleoplasty may result in little to no difference in neck pain intensity (VAS: 0 mm-10 mm scale) at short-term (2 RCTs, MD 0.33, 95% CI -0.36 to 1.03), medium-term (1 RCT, MD 0.40, 95% CI -0.12 to 0.92) and long-term follow-up (1 RCT, MD 1.19, 95% CI -0.28 to 2.66) and for neck-related functional status (NDI) at short-term (1 RCT, MD -0.69, 95% CI -12.63 to 11.25) and medium-term (1 RCT, MD -0.22, 95% CI -12.31 to 11.87) as well.

The evidence is very uncertain about the effect of nucleoplasty compared to surgery on recovery 3, 6 and 12 months after treatment (1 RCT, RR 0.81, 95% CI 0.51 to 1.29; 1 RCT, RR=0.83, 95% CI 0.47 to 1.46 and 1 RCT, RR=0.71, 95% CI 0.44 to 1.14, respectively).

There was low-certainty evidence about the risk of adverse effects between the two treatments.

This study did not report on work-related disability and psycho-social outcomes.

Authors' conclusions

Based on the studies we found, there was low-certainty of evidence that nucleoplasty may reduce pain intensity and improve global health status-physical functioning at long-term follow-up compared to conservative treatment. Both of these results reached clinical relevance. For all the other outcomes and comparisons the evidence was low to very low. Included studies were all of high risk of bias.

Plain language summary

Nucleoplasty for cervical radicular pain due to a disc herniation

Background

CRP due to a disc herniation is a common diagnosis with various treatment options available. It is characterised by nerve compression from herniated disc material or arthritic bone spurs and can produce pain, numbness, sensory deficits, or motor dysfunction in the neck and arms.

Nucleoplasty is a minimally invasive treatment that is used to treat the herniated disc. During nucleoplasty, the specialist uses image guidance to remove a small amount of disc tissue to relieve pressure on the pinched nerve to reduce pain and restore mobility.

Candidates for nucleoplasty include people who have severe pain due to a disc herniation for at least three months and who have failed conservative treatment such as rest, pain medication, physiotherapy, a cervical collar, or a combination of these.

The aim of this review was to find out the effectiveness of nucleoplasty on pain intensity of the arm and neck, neck-related functional status, recovery, global health status, work-related disability, psycho-social outcomes and adverse effects compared to no treatment or placebo treatment, conservative treatment, non-surgical interventions and surgery in patients with CRP due to a disc herniation.

What did we look for?

We looked for studies published up to October 5th, 2021 that:

- were randomised controlled trials (RCTs), medical studies where participants are randomly put into one of two or more treatment groups. This type of study provides the most reliable evidence whether a treatment makes a difference;
- were non-randomized controlled trials (NRCTs), medical studies in which the participants are not assigned by chance to different treatment groups. Participants may choose which group they want to be in, or they may be assigned to the groups by the researchers. Therefore, this type of study gives less reliable evidence whether a treatment makes a difference than a RCT.

What did we find?

We found four RCTs (272 participants) and two NRCTs (129 participants) that included patients with CRP due to a disc herniation. All participants of the included studies were adults, aged from 16 to 65 years. They were treated in a hospital or a clinic. Three studies (one RCT and two NRCTs) compared nucleoplasty to conservative treatment. One RCT compared nucleoplasty to a non-surgical intervention (pulsed radio frequency

of the dorsal root ganglion) and two RCTs compared nucleoplasty to surgery, i.e. anterior discectomy and open discectomy.

Study participants were then followed for a period of time after treatment, this varied from 3 months to 12 months after treatment.

Key Results

There is little to suggest that nucleoplasty is an effective treatment for people with CRP due to a disc herniation.

Nucleoplasty versus no treatment or placebo

We did not find any RCT or NRCT on this comparison.

Nucleoplasty versus conservative treatment

We do not know whether nucleoplasty reduces average pain intensity compared to conservative treatment, because this has been studied in too few people. We found two NRCTs, however these studies were very poorly conducted, and therefore we could not use them to assess the effectiveness of this comparison. We found some evidence of one RCT that nucleoplasty may reduce pain intensity and may improve global health status-physical functioning at long-term follow-up, but not at shorter term.

Nucleoplasty versus pulsed radio frequency of the dorsal root ganglion

We do not know whether nucleoplasty reduces average pain intensity compared to pulsed radio frequency, because there was only one RCT with very few people. Nucleoplasty make little to no difference on pain intensity at short-term follow-up compared to pulsed radio frequency of the dorsal root ganglion.

Nucleoplasty versus surgery

We do not know whether nucleoplasty reduces average pain intensity compared to discectomy, because there were only two RCTs with few people. Nucleoplasty make little to no difference on pain intensity at short-term and medium-term compared to discectomy.

Certainty of evidence

Based on studies we found, the certainty of evidence was low to very low for all outcomes. This was due to poor study designs, inconsistency and imprecision in the results.

SUMMARY OF FINDINGS

1. Summary of findings table - nucleoplasty vs. conservative treatment for patients with cervical radicular pain due to a disc herniation

Patient or population: patients with cervical radicular pain due to a disc herniation
Setting: Clinic for neurosurgery
Intervention: nucleoplasty
Comparison: conservative treatment

Outcomes	Anticipated absolute effects* (95% CI)					
	Risk with conservative treatment	Risk with nucleoplasty	Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
Pain intensity assessed with: VAS Scale from: 0 mm to 100 mm follow-up: 3 months	The mean pain intensity was **-30.45**	MD **22.71 lower** (30.1 lower to 15.32 lower)	-	120 (1 RCT)	⨁⨁⨀⨀ Low[a,b]	Compared to conservative treatment, nucleoplasty may result in a slight reduction in pain intensity 3 months after treatment.
Pain intensity assessed with: VAS Scale from: 0 mm to 100 mm follow-up: 6 months	The mean pain intensity was **-40.26**	MD **15.96 lower** (23.15 lower to 8.77 lower)	-	118 (1 RCT)	⨁⨁⨀⨀ Low[a,b]	Compared to conservative treatment, nucleoplasty may result in little to no difference in pain intensity 6 months after treatment.
Pain intensity assessed with: VAS Scale from: 0 mm to 100 mm follow-up: 12 months	The mean pain intensity was **-36.45**	MD **29.28 lower** (36.4 lower to 22.16 lower)	-	118 (1 RCT)	⨁⨁⨀⨀ Low[a,b]	Compared to conservative treatment, nucleoplasty may reduce pain intensity 12 months after treatment.
Neck-related functional status assessed with: NDI Scale from: 0 to 50 follow-up: 3 months	The mean neck-related functional status was **-9.27**	MD **2.48 lower** (5.11 lower to 0.15 higher)	-	120 (1 RCT)	⨁⨁⨀⨀ Low[a,c]	Compared to conservative treatment, nucleoplasty may result in little to no difference in neck-related functional status 3 months after treatment.
Neck-related functional status assessed with: NDI Scale from: 0 to 50 follow-up: mean 6 months	The mean neck-related functional status was **-12.86**	MD **0.5 lower** (3.2 lower to 2.2 higher)	-	118 (1 RCT)	⨁⨁⨀⨀ Low[a,c]	Compared to conservative treatment, nucleoplasty may result in little to no difference in neck-related functional status 6 months after treatment.

Outcomes	Anticipated absolute effects* (95% CI)					
	Risk with conservative treatment	Risk with nucleoplasty	Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
Neck-related functional status assessed with: NDI follow-up: 12 months	The mean neck-related functional status was **-12.40**	MD **4.3 lower** (6.38 lower to 1.77 lower)	-	118 (1 RCT)	⨁⨁⊖⊖ Low[a,c]	Compared to conservative treatment nucleoplasty may result in little to no difference in neck-related functional status 12 months after treatment.
Recovery - not measured	-	-	-	-	-	
Global health status - not measured	-	-	-	-	-	
Work-related disability - not measured	-	-	-	-	-	
Psycho-social outcomes - not measured	-	-	-	-	-	
Adverse effects follow-up: 12 months	0 per 1000	**0 per 1000** (0 to 0)	Not estimable	120 (1 RCT)	⨁⊖⊖⊖ Very low[a,d]	The evidence is very uncertain about the effect of cervical nucleoplasty on adverse effects.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **MD:** mean difference

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

See interactive version of this table: https://gdt.gradepro.org/presentations/#/isof/isof_question_revman_web_418055082937770642.

Footnotes
[a] Serious risk of bias: unclear description of randomization proces and allocation concealment; lack of blinding of participants, health care providers and outcome assessors.
[b] Serious imprecision: small sample size; CI includes possibility of a large as well as a small reduction in pain.
[c] Serious imprecision: small sample size; CI includes possibility of an effect in favor of nucleoplasty and an effect in favor of conservative treatment.
[d] Very serious imprecision: no events in both groups, small sample size.

2. Summary of findings table - Nucleoplasty compared to pulsed radio frequency of the dorsal root ganglion for patients with cervical radicular pain due to a disc herniation

Patient or population: patients with cervical radicular pain due to a disc herniation
Setting: Hospital
Intervention: nucleoplasty
Comparison: pulsed radio frequency of the dorsal root ganglion

	Anticipated absolute effects* (95% CI)					
Outcomes	**Risk with pulsed radio frequency of the dorsal root ganglion**	**Risk with nucleoplasty**	**Relative effect (95% CI)**	**№ of participants (studies)**	**Certainty of the evidence (GRADE)**	**Comments**
Pain intensity assessed with: VAS Scale from: 0 mm to 100 mm follow-up: 3 months	The mean pain intensity was **35.5**	MD **7.9 lower** (29.45 lower to 13.65 higher)	-	57 (1 RCT)	⊕⊖⊖⊖ Very low[a,b]	Compared to pulsed radio frequency of the dorsal root ganglion, nucleoplasty may result in little to no difference in pain intensity 3 months after treatment.
Neck-related functional status assessed with: NDI follow-up: 3 months	The mean neck-related functional status was **10.8**	MD **0.3 higher** (6.97 lower to 7.57 higher)	-	57 (1 RCT)	⊕⊖⊖⊖ Very low[a,b]	Compared to pulsed radio frequency of the dorsal root ganglion, nucleoplasty may result in little to no difference on neck-related functional status 3 months after treatment.
Recovery assessed with: VAS patient satisfaction Scale from: 0 mm to 100 mm follow-up: 3 months	The mean recovery was **63.5**	MD **5.1 lower** (29.92 lower to 19.72 higher)	-	57 (1 RCT)	⊕⊖⊖⊖ Very low[a,c,d]	Compared to pulsed radio frequency of the dorsal root ganglion, nucleoplasty may result in little to no difference on recovery 3 months after treatment.
Global health status - not measured	-	-	-	-	-	
Work-related disability - not measured	-	-	-	-	-	

Outcomes	Anticipated absolute effects* (95% CI) Risk with pulsed radio frequency of the dorsal root ganglion	Risk with nucleoplasty	Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
Psycho-social outcomes - not measured	-	-	-	-	-	
Adverse effects follow-up: 3 months	18 per 100	**18 per 100** (4 to 56)	**OR 1.00** (0.17 to 5.83)	34 (1 RCT)	⊕⊖⊖⊖ Very low[a,e]	The evidence is very uncertain about the risk of adverse effects for nucleoplasty compared to pulsed radio frequency of the dorsal root ganglion, 3 months after treatment.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **MD:** mean difference; **OR:** odds ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

See interactive version of this table: https://gdt.gradepro.org/presentations/#/isof/isof_question_revman_web_418066672338171739.

Footnotes
[a] Serious risk of bias: allocation concealment and blinding of health care providers unclear; high risk of attrition bias because of possible selective follow up.
[b] Very serious imprecision: very small sample size; CI includes possibility of a large effect in favor of nucleoplasty and small, not important effect in favor of pulsed radio frequency of the dorsal root ganglion.
[c] Serious indirectness: patient satisfaction is surrogate outcome for recovery.
[d] Very serious imprecision: very small sample size CI includes possibility of appreciable lower chance of recovery for nucleoplasty and an appreciable higher chance of recovery for pulsed radio frequency of the dorsal root ganglion.
[e] Very serious imprecision: very small sample size. CI includes possibility of a large effect in favor of nucleoplasty and a large effect in favor of PRF

3. Summary of findings table - Nucleoplasty compared to surgery for patients with cervical radicular pain due to a disc herniation

Patient or population: patients with cervical radicular pain due to a disc herniation
Setting: Hospital single centre
Intervention: nucleoplasty
Comparison: surgery

	Anticipated absolute effects* (95% CI)					
Outcomes	**Risk with surgery**	**Risk with nucleoplasty**	**Relative effect (95% CI)**	**№ of participants (studies)**	**Certainty of the evidence (GRADE)**	**Comments**
Arm pain intensity assessed with: VAS 0-10mm follow-up: 3 months	Inconsistent effects between the 2 RCTs: mean difference in pain -0.90 (95% CI -1.41 to -0.39) and 0.80 (95% CI -0.79 to 2.39), I-square 75%			105 (2 RCTs)	⊕⊖⊖⊖ Very low[a,b,c]	The evidence is very uncertain about the effect of nucleoplasty on arm pain intensity.
Arm pain intensity assessed with: VAS Scale from: 0 to 10 follow-up: 6 months	The mean arm pain intensity was **1.6**	MD **0.7 higher** (0.36 higher to 1.04 higher)	-	57 (1 RCT)	⊕⊕⊖⊖ Low[a,c]	Compared to open discectomy, nucleoplasty may result in little to no difference in arm pain intensity 6 months after treatment.
Arm pain intensity assessed with: VAS Scale from: 0 to 10 follow-up: 12 months	The mean arm pain intensity was **2.4**	MD **0.7 higher** (0.84 lower to 2.24 higher)	-	48 (1 RCT)	⊕⊕⊖⊖ Low[a,c]	Compared to anterior cervical discectomy, nucleoplasty may result in little to no difference in arm pain intensity 12 months after treatment.
Neck pain intensity assessed with: VAS Scale from: 0 to 10 follow-up: 3 months	The mean neck pain intensity was **2.6**	MD **0.33 higher** (0.36 lower to 1.03 higher)	-	105 (2 RCTs)	⊕⊕⊖⊖ Low[a,c]	Compared to surgery, nucleoplasty may result in little to no difference in neck pain intensity 3 months after treatment.
Neck pain intensity assessed with: VAS Scale from: 0 to 10 follow-up: 6 months	The mean neck pain intensity was **1.9**	MD **0.4 higher** (0.12 lower to 0.92 higher)	-	57 (1 RCT)	⊕⊕⊖⊖ Low[a,c]	Compared to open discectomy, nucleoplasty may result in little to no difference in neck pain intensity 6 months after treatment.
Neck pain intensity Scale from: 0 to 10 follow-up: 12 months	The mean neck pain intensity was **2.3**	MD **1.19 higher** (0.28 lower to 2.66 higher)	-	48 (1 RCT)	⊕⊕⊖⊖ Low[a,c]	Compared to anterior cervical discectomy, nucleoplasty may result in little to no difference in neck pain intensity 12 months after treatment.

Outcomes	Anticipated absolute effects* (95% CI) Risk with surgery	Risk with nucleoplasty	Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
Neck-related functional status Scale from: 0 to 100 follow-up: 3 months	The mean neck-related functional status was **49.79**	MD **0.69 lower** (12.63 lower to 11.25 higher)	-	48 (1 RCT)	⨁⨁⨀⨀ Low[a,c]	Compared to anterior cervical discectomy, nucleoplasty may result in little to no difference in neck-related functional status 3 months after treatment.
Neck-related functional status Scale from: 0 to 100 follow-up: 12 months	The mean neck-related functional status was **46.35**	MD **0.22 lower** (12.31 lower to 11.87 higher)	-	48 (1 RCT)	⨁⨁⨀⨀ Low[a,c]	Compared to anterior cervical discectomy, nucleoplasty may result in little to no difference in neck-related functional status 12 months after treatment.
Recovery assessed with: Patient completely satisfied follow-up: 3 months	67 per 100	**54 per 100** (34 to 86)	**RR 0.81** (0.51 to 1.29)	48 (1 RCT)	⨁⨀⨀⨀ Very low[a,c,d]	The evidence is very uncertain about the effect of nucleoplasty compared to open discectomy on recovery 3 months after treatment.
Recovery assessed with: Patient completely satisfied follow-up: 6 months	50 per 100	**42 per 100** (24 to 73)	**RR 0.83** (0.47 to 1.46)	57 (1 RCT)	⨁⨀⨀⨀ Very low[a,c,d]	The evidence is very uncertain about the effect of nucleoplasty compared to open discectomy on recovery 6 months after treatment.
Recovery assessed with: Patient completely satisfied follow-up: 12 months	71 per 100	**50 per 100** (31 to 81)	**RR 0.71** (0.44 to 1.14)	48 (1 RCT)	⨁⨀⨀⨀ Very low[a,c,d]	The evidence is very uncertain about the effect of nucleoplasty compared to anterior cervical discectomy on recovery 12 months after treatment.
Global health status - not measured	-	-	-	-	-	
Work-related disability - not measured	-	-	-	-	-	

Outcomes	Anticipated absolute effects* (95% CI) Risk with surgery	Risk with nucleoplasty	Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
Psycho-social outcomes - not measured	-	-	-	-	-	
Adverse effects follow-up: range 6 months to 12 months	In 1 RCT (n=70, follow up 6 months) no discitis, infection and hematoma were observed. In the nucleoplasty group one patient was operated again and one patient still suffered from cervical pain after 6 months. One patient in surgery group suffered from radicular pain 6 months after the operation. In the other RCT (n=48, follow up 12 months) 3 patients in the surgery group experienced adverse effects sdirectly related to the operation. In the nucleoplasty group no adverse events occured directly related to the procedure.			105 (2 RCTs)	⨁⨁⊖⊖ Low[a,c]	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **MD:** mean difference; **RR:** risk ratio; **SMD:** standardised mean difference

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

See interactive version of this table: https://gdt.gradepro.org/presentations/#/isof/isof_question_revman_web_418049159467441286.

Footnotes
[a] Serious risk of bias: high risk of outcome detection bias because lack of blinding participants, health care providers and outcome detectors.
[b] Serious inconsistency: high I-square, opposing direction of effects and minimal overlap in CIs.
[c] Serious imprecision: small sample size.
[d] Serious indirectness: patient satisfaction is surrogate outcome for recovery

Background

Cervical radicular pain (CRP) is a common diagnosis with various treatment options available. In neurologically stable patients, various forms of conservative treatment are prescribed, such as rest, analgesics and non-steroidal anti-inflammatory drugs, physiotherapy, a cervical collar, or a combination of these. Conservative treatment leads to a spontaneous reduction of pain and disability in 40% of patients (Lees 1963; Dillin 1986). One study evaluated the effects of conservative treatment for cervical radicular syndrome, and concluded that in the early phase of this disease a semi-hard cervical collar and rest or physiotherapy reduced neck and arm pain, compared to a 'wait and see' policy (Kuijper 2009).

When conservative treatment fails and symptoms persist or increase in severity, surgical treatment is considered (Nardi 2005). The goals of surgery are to alleviate pressure on the affected cervical spinal nerve and the roots of the nerve, and if necessary to restore vertebral alignment and spine stabilization. The affected disc will be removed during the surgical procedure, with or without fusing of the two adjacent vertebral bodies. Bone grafts can be used to stimulate the fusion process (Jacobs 2012). This surgical technique has been widely accepted as the standard treatment for CR for more than five decades. However, this procedure is associated with a small risk of serious complications such as perforation of the oesophagus, injuries to the carotid or vertebra and severe neurological complications. The results of surgery are not always satisfactory and the overall outcome may be similar to conservative treatment (Nikolaidis 2010; Gebremariam2012; van Middelkoop 2013). Currently, there is an evolving trend in all spinal surgery toward less invasive techniques. Nucleoplasty is a minimally invasive technique, and is a treatment which uses radiofrequency technology for percutaneous disc decompression.

Description of the condition

There is no universally accepted definition of CRP (Thoomes 2012). It is defined by Carette and Fehlings as a neurologic condition characterised by dysfunction of a cervical spinal nerve, the roots of the nerve, or both. It usually presents with pain in the neck and one arm, with a combination of sensory loss, loss of motor function, or reflex changes in the affected nerve-root distribution (Carette 2005). Some authors indicate that CRP must be distinguished from CR (Van Zundert 2010). In CR there is a clear loss of sensory and/or motor function, while radicular pain is characterised by the formation of ectopic pulses. These two disorders can also coexist and may be caused by the same anatomical changes such as intervertebral disc herniation, radiculitis due to arthritis, narrowing of the intervertebral foramen, infection, or inflammatory exudates. Radicular pain can deteriorate into CR due to disease progression (Van Zundert 2010).

The epidemiological data on CR are minimal. In a retrospective population-based study from Rochester, Minnesota in the United States (1976 to 1990) the annual incidence of CR was 83 per 100,000 people. The annual incidence rate was 107.3 per 100,000 for men and 63.5 per 100,000 for women (Radhakrishnan 1994). A door-to-door survey in a Sicilian municipality reported a prevalence of 3.5 per 1000 person-years (Salemi 1996). Both studies found an association between age and the development of CR, with a peak incidence in the sixth decade of life for people of both genders (Radhakrishnan 1994; Salemi 1996). In an epidemiological review of a population of American soldiers (2000 to 2009) the incidence of CR was 1.79 per 1000 person-years. The incidence was calculated from a prospectively-collected military database, which includes more than 20,000 cases of CR from an ethnically- and socio-economically diverse cohort. The annual incidence rate was 1.76 per 1000 person-years for men and 1.95 per 1000 person-years for women (Schoenfeld 2012). Age is an important risk factor for developing CR (Radhakrishnan 1994; Salami 1996; Schoenfeld 2012) and that females have a greater risk of developing CR than males (Schoenfeld 2012).

Description of the intervention.

In 2000, the United States of America's Food and Drug Administration approved nucleoplasty as a treatment for contained disc herniations (Gerges 2010). Nucleoplasty is a minimally invasive technique, which uses coagulation and tissue ablation for percutaneous disc decompression. Radiofrequency energy is applied to a conductive medium (a one mm diameter bipolar instrument) and forms a highly focused plasma field around the energised electrodes. This plasma field contains highly ionised particles, which break organic molecular bonds and form small channels within the nucleus pulposus tissue, resulting in decompression of the herniated disc. By-products such as low-molecular-weight inert gases and elementary molecules are removed via the needle (Chen 2003). The removal of disc tissue is a non-heat-driven process and is associated with temperatures of between 40 ℃ to 70 ℃. In this way the integrity of the surrounding healthy tissue is preserved. Approximately one mL of disc tissue volume is removed, which corresponds with a reduction of the discal volume by 10% to 20% (Gerges 2010). One study examined the effect of nucleoplasty on the tissue and its authors concluded that volumetric removal of the nucleus pulposus tissue can be performed without disruption or necrosis of non-targeted nucleus, annulus, endplate, nerve root or spinal cord (Chen 2003). This is supposed to down-regulate local inflammatory mediators, reduce disc size, and stimulate the healing process (Chen 2003).

How the intervention might work

The primary goal of nucleoplasty is volumetric reduction of the tissue of the nucleus pulposus, which is vaporised at lower temperatures and causes a decrease in

intradiscal pressure of the herniated disc. Several studies have demonstrated that cervical nucleoplasty is a safe and effective technique (Gerszten 2006; Birnbaum 2009; Sim 2011; Halim 2013). A recent observational study showed that complete or partial long-term pain relief can be safely achieved using nucleoplasty in patients with a contained cervical herniated disc (Halim 2013). In the vast majority of these patients, nucleoplasty achieves a long-term reduction in pain, good clinical outcomes, reduced pain medication use, and higher patient satisfaction (Halim 2013).

Careful selection of patients is important for successful nucleoplasty (Gerges 2010 ; Halim 2013). Patients with incomplete annular tears and minimally degenerated discs may benefit the most (Gerges 2010; Halim 2013). Compared to surgical treatment, nucleoplasty is a minimally invasive percutaneous technique performed on an outpatient basis with a fast recovery time. There have been no neurological complications reported from the procedure itself, although this claim is subject to publication bias. Until now, very limited evidence has been found on the effects of nucleoplasty in patients with CR.

Why is it so important to do this review

When the severe symptoms of patients with CRP due to a disc herniation do not improve with conservative treatment, surgical treatment is considered. Surgery comes with risks, reoperation rates are significant (Veeravagu 2014) and pain relief is not guaranteed. Long-term pain medication and other forms of conservative treatment carry their own risks and costs. We would consider it an important improvement for the patient, if the same benefits of surgery could be achieved with nucleoplasty, without serious complications and at reduced cost. At present, there is only one systematic review available focusing on nucleoplasty treatment options for people with CRP due to a disc herniation (Wullems 2014), which did not use the GRADE approach to measure the quality of evidence. The Wullems review assessed the risk of bias of the randomised clinical trials (RCTs) using the method described by Furlan et al. (Furlan 2015) and the non-RCTs using the Newcastle-Ottawa Scale (NOS). However, they included two non-RCTS (Birnbaum 2009; Nardi 2005) as RCTs. We will perform an update of their review and use the current guidance for risk of bias and certainty of evidence according to the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011). We will also measure psycho-social outcomes as secondary outcomes.

Objectives

To determine whether nucleoplasty improves clinical and functional outcomes compared to surgery or conservative treatment for patients with cervical radicular pain due to a disc herniation.

Methods

Criteria for considering studies for this review

Types of studies

We included full journal publications of quantitative studies, namely randomised controlled trials (RCTs), quasi-randomised controlled trials (using a method of allocating people to a treatment that is not strictly random, e.g. by date of birth, alternation) and non-randomised controlled trials (NRCTs).

Types of participants

We included studies involving adults (18 years of age or older), with cervical radicular pain due to single level degenerative disc disease of the cervical spine corresponding to the affected level. We included degenerative disc diseases such as a narrowing of the intervertebral foramen, intervertebral disc herniations and radiculitis due to the degenerative effect of arthritis. The duration of symptoms must be at least six weeks, with insufficient relief of symptoms with conservative treatment. We excluded studies involving patients with previous surgery of the cervical spine, inflammatory spinal arthritis and malignancy of the cervical spine region.

Types of interventions

We included studies with nucleoplasty as the index treatment.

The index treatment has been compared with:

- No treatment or placebo treatment;
- Conservative treatment (such as oral medication (e.g. non-steroidal anti-inflammatory drugs, muscle relaxants), physiotherapy, manual therapy, bed rest, cervical collar or traction);
- Minimally invasive interventions (pulsed radio frequency of the dorsal root ganglion);
- Surgery (anterior and posterior decompression, either with non-fusion techniques; fusion techniques by plate, cage, autograft, allograft material, or artificial disc; or a combination).

Types of outcome measures

We collected all outcome data at short-term follow-up (up to and including 3 months), medium-term follow-up (more than 3 and less than 12 months) and long-term follow-up (1 year or longer).

Primary outcomes

- Pain intensity of the arm and neck expressed on a visual analogue scale or other measure of pain scale (e.g. visual analogue scale for pain (Sriwatanakul 1983), ordinal scale (Von Korff 2000)).

- Neck-related functional status, expressed on a neck-specific scale, e.g. Neck Disability Index (Vernon 2008).
- Recovery measured by global perceived effect (e.g. proportion of patients recovered, subjective improvement of symptoms).

Clinical relevance
There is a lack of studies to determine the clinical relevance of treatment effectiveness between group differences, also known as the minimal clinically important difference (MCID) in patients with CRP due to a disc herniation. There is some consensus on the Minimal Clinically Important Change (MCIC) in the literature, which refers to the improvement of health status in patients. In this review, we consider the MCIC as a valuable measure to define the MCID. There is some consensus in the literature that the MCIC for pain on a visual analog scale (VAS) ranges from 20 mm to 30 mm (Carreon 2010; Ostelo 2005; Lee 2003). A clinical study with a study population fairly similar to ours, i.e. patients undergoing cervical spine fusion due to degenerative conditions, found a MCIC of 25 mm for neck pain and arm pain and an MCIC of 7.5 for the neck disability index (Carreon 2010). In this review, we will use this value of the MCIC to choose the MCID.

We consider a between-group difference of 25 mm for neck pain and arm pain as clinically relevant and for the neck disability index we find a between-difference of 7.5 as clinically relevant (Carreon 2010).

For recovery, we used dichotomous outcomes; if there were categories in range of improvement, we counted categories such as ''almost recovered' and 'completely recovered', 'good', and 'very good or excellent', and 'a lot' to 'complete recovery' responses as recovered.

Secondary outcomes:
- Overall health status e.g. The Short Form (36) Health Survey (Ware 1992), EuroQoL 5D (Williams 1990), Sickness Impact Profile (De Bruin 1994).
- Work-related disability (rate of health-related absenteeism or unemployment).
- Psycho-social outcomes (e.g. anxiety, depression, pain behaviour).
- Adverse effects (totality of possible adverse consequences of an intervention or therapy such as early adverse events and delayed complications).

Clinical relevance
We evaluated overall health status (SF-36) as a continuous outcome and considered a between-group difference of 4.1 as clinically relevant (Carreon 2010).

For work-related disability, psycho-social outcomes and adverse effects, we used dichotomised outcomes, usually proportion of participants.

Search methods for identification of studies

Electronic searches

We searched the following databases with no language restrictions from inception to October 5th, 2021 for relevant studies:

- CENTRAL (The Cochrane Central Register of Controlled Trials; from 1992 to October 5th, 2021)
- MEDLINE (Medical Literature Analysis and Retrieval System Online, Epub Ahead of Print, In-Process & Other Non-Indexed Citations, OVID MEDLINE(R) Daily and Ovid MEDLINE(R):OvidSP; from 1946 to October 5th, 2021)
- EMBASE (Excerpta Medica Database, Elsevier, Embase.com 1971 to October 5th, 2021)
- CINAHL(Cumulative Index to Nursing and Allied Health Literature, EBSCO, 1981 to October 5th, 2021)
- Web of Science Core Collection (Thomson Reuters, Web of Knowledge 1900 to October 5th, 2021)
- Scopus (Elsevier, scopus.com 1966 to October 5th, 2021)
- PEDro (Physiotherapy Evidence Database) to October 5th, 2021
- ClinicalTrials.gov to October 5th, 2021
- World Health Organisation (WHO) International Clinical Trials Registry Platform (ICTRP) to October 5th, 2021
- Google Scholar to October 5th, 2021

We did not use an RCT filter in our electronic searches, as the set of intervention terms limited the results sufficiently. In 2021, we searched CENTRAL and the CBN trials register in CRS (Cochrane Register of Studies) Web; previously they were searched in CRS standalone.

Search strategies can be found in Appendix 1. No language restrictions were applied. Methods are in line with the guidelines of the Cochrane Handbook (Lefebvre 2019).

Searching other resources

We searched the System for Information on Grey Literature (SIGLE) database through OpenSigle, subheading biological and medical sciences, to search for trials that might have been missed by other sources. We also consulted personal files, screen references, and communicated with the Cochrane Back and Neck Group and content experts to identify additional studies.

Data collection and analyses

Selection of studies

Two authors (JDdR and BSH) screened the titles and abstracts of all studies retrieved by the searches and next the full text of all potentially eligible articles to identify those meeting the inclusion criteria. The authors selected the studies independently and discussed the results to make the final selection. In case of disagreement, they consulted with a third author (JGG). We did not use language restrictions. Study flow diagrams, following the template described in the PRISMA statement (Liberati 2009), were used to present the results of the search and the process of screening and selecting studies for inclusion in the review.

Data extraction and management

Two authors (JDdR and ML) independently extracted the data from each included trial using a standard form. These authors also pilot tested the standardised form on a sample of three articles not included in the review. ML and AV independently extracted the data from the RCT of JDdR et al. (De Rooij 2020).

The following data has been extracted from each study: study design, characteristics of the study population (e.g. number of participants, age, gender, nature and duration of the health problem, inclusion and exclusion criteria), study characteristics (e.g. country, recruitment modality, setting and company sponsorship, risk of bias), description of the experimental and control interventions, co-interventions, duration of follow-up, outcomes assessed, and results. The two authors discussed any disagreement and consult a third review author if necessary.

Assessment of risk of bias in included studies

Randomised controlled trials (RCTs)

We assessed risk of bias for the included RCTs using the Cochrane's Risk-Of-Bias tool for randomized trials (Higgins 2011). We based the overall bias judgement of included RCTs on the following five domains: selection bias, performance bias, attrition bias, detection bias and selective reporting. An RCT at low risk on all of these domains was labelled as a low-risk study. An RCT at high risk on one of these domains was labelled as a high-risk study. If there was no clear information on the risk of bias for one or more key domains, but the RCT was not at high risk for any domain, we indicated that the risk of bias in the study was unclear. The sources of risk of bias are provided in Table 1 and how we reached our judgment of "Yes" for the sources of risk of bias is shown in Table 2.

Non-randomised controlled trials (NRCTs)

We assessed the risk of bias of the included NRCTs using the Risk Of Bias In Non-randomized Studies - of Interventions (ROBINS-I) tool (Sterne 2016). Using the ROBINS-I tool, we assessed the risk of bias of studies based on the following seven domains:

bias due to confounding (i.e confounding by indication by the neurosurgeon), bias in selection of participants into the study, bias in classification of interventions, bias due to deviations from the intended intervention, bias due to missing data, bias in measurement of outcomes and bias in selection of the reported result.

Our 'Risk of bias' judgements led to labelling the studies on these domains as 'critical risk', 'serious risk', 'moderate risk', 'low risk', or 'no information'. How we reached our 'Risk of bias' judgements for the pre-intervention and at-intervention domains is shown in Table 3, and how we reached these judgements for post-intervention domains is provided in Table 4.

Two review authors (JDdR and ML) independently assessed the risks of bias of all included studies. In case of disagreement, they consulted a third author (APV). We asked additional information from authors of the studies regarding any items that remained unclear.

The additional details on quality assessment for each outcome are described in the Data synthesis section and Appendix 2.

Measures of treatment effect

Dichotomous outcomes have been analysed by calculating the relative risk (RR). Continuous outcomes (e.g. visual analogue scale, numeric rating scale) have been analysed by calculating the mean difference (MD) when the same instrument is used to measure outcomes, or the standardised mean difference (SMD) when different instruments are used to measure outcomes. The SMD expresses the size of the intervention effect in each study relative to the variability observed in that study. The uncertainty will be expressed with 95% confidence intervals (95% CI). For each treatment comparison, we calculated an effect size and a 95% CI.

Unit of analysis issues

We did not identify unit of analysis issues with regard to cross-over or cluster randomised trials. However, we found repeated observations on participants in most of the eligible studies. In this case we followed the suggested strategy of defining the outcomes (already stated above) as well as the time points a priori (Higgins 2011). The time points are short-term follow-up (up to and including 3 months), medium-term follow-up (more than 3 and less than 12 months) and long-term follow-up (12 months or longer). When there were multiple time points that fall within the same category, the time points that were closest to the end of the treatment, and to 6 months and 12 months were used. If studies include multiple treatment arms and, therefore, multiple comparisons, we selected the most appropriate comparison. If two groups were considered to be the same (e.g. 2 controls: waiting list and no treatment) the 'shared' intervention was split in order to include two (reasonably independent) comparisons.

Dealing with missing data

When standard deviations (SDs) were not reported or could not be acquired from the study authors we used one of the following three options: calculation of the missing SDs from other reported data (e.g. mean differences, P values, number of observations); if graphs with error bars were available we measured them manually and impute by taking the SD of similar sized studies for that outcome. Finally, if no measure of variation was reported in the text, we estimated the SD based upon other studies with a similar population and risk of bias.

Assessment of heterogeneity

To assess heterogeneity, we visually inspected the forest plots and calculated the I^2 statistic for each pooled analyses, as recommended by the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

In concordance with Cochrane guidelines, we planned to only perform a meta-analysis when a group of studies was sufficiently homogeneous to provide a meaningful summary. In case of heterogeneity, we decided to perform a narrative data synthesis.

Assessment of reporting biases

When there are more than 10 studies on the same outcome measure, we created and used funnel plots to assess publication bias.

Data synthesis

We grouped the analyses separately according to the control interventions, the outcomes measured, and the timing of outcome assessment. The outcome measures from the individual studies have been combined through meta-analysis where possible (clinical homogeneity concerning population, intervention and outcomes between trials). Because of the low number of studies, meta-analysis was not possible, and we described the results narratively.

Subgroup analysis and investigation of heterogeneity

We could not perform subgroup analyses for the primary outcome (i.e. pain intensity of the arm and neck expressed on a visual analogue scale or other measure of pain scale) to investigate the potential influence of trial characteristics, i.e. to investigate the effects of different control groups, different degenerative disc diseases, location of the health problem (neck versus arm) and the duration of the problem (chronic versus (sub) acute) due to a lack of studies.

Sensitivity analysis

We planned a sensitivity analysis to assess the influence of including trials at high risk of bias. We defined a trial meeting fewer than five criteria in the 'Risk of bias' analysis as being at high risk of bias. We also planned a second sensitivity analysis to investigate the

influence of high levels of attrition (15% or more participants lost to follow up). However, we could not perform this sensitivity analysis because of the low number of studies.

Summary of findings and assessment of the certainty of the evidence

The overall certainty of the evidence was evaluated using the GRADE approach (Guyatt 2011). The certainty of the evidence for a specific outcome was based on 1) study limitations (due to risk of bias), 2) inconsistency, 3) indirectness (i.e. generalisability), 4) imprecision (sufficient data with narrow confidence intervals) and 5) other (e.g. publication bias).

We used GRADEpro GDT software to construct a 'Summary of findings table' (GRADEpro GDT 2015).

Results

Description of studies

We have described the characteristics of the six included studies in the Characteristics of included studies table (Table 5).

Results of the search

The electronic searches from the inception to October 5th, 2021 identified 1426 records (Figure 1). After we removed duplicates (595 studies), we screened 831 studies for title and abstract. Following full-text assessment, both review authors (JDdR and BSH) agreed that 6 studies were eligible for inclusion (Abrishamkar 2018; Birnbaum 2009; Cesaroni 2010; De Rooij 2020; Halim 2016; Nardi 2005). There are no ongoing studies or studies awaiting classification.

Included studies

We included four studies with a RCT design (Abrishamkar 2018; Cesaroni 2010; De Rooij 2020; Halim 2016) and two studies with an NRCT design (Birnbaum 2009; Nardi 2005). All of these studies used a two-group design to compare their interventions.

Sample size

The sample size of the individual studies ranged from 34 to 120 participants. A total of 401 participants were included in the six studies. All included studies reported withdrawal or dropout rates, which ranged from 1% (Nardi 2005) to 26% (Halim 2016) for any time of follow-up.

Setting

All six studies (Abrishamkar 2018; Birnbaum 2009; Cesaroni 2010; De Rooij 2020; Halim 2016; Nardi 2005) were conducted in an outpatient basis setting.

Participants

All participants of the studies were adults, aged from 16 to 65 years. The mean or median age of the participants ranged from 23 (Birnbaum 2009) to 59 years (Halim 2016). Five studies included a homogeneous population of participants with magnetic resonance imaging (MRI) proven single-level contained herniated cervical disc (Cesaroni 2010; De Rooij 2020; Halim 2016; Nardi 2005). One study also included participants with a single-level contained herniated cervical disc, however they did not mention that they performed an MRI (Abrishamkar 2018).

Interventions

Three studies compared nucleoplasty to conservative treatment (Birnbaum 2009; Cesaroni 2010; Nardi 2005). One study compared nucleoplasty to pulsed radio frequency (PRF) of the dorsal root ganglion (DRG) (Halim 2016) and two studies compared nucleoplasty to surgery, i.e. open discectomy and anterior discectomy (Abrishamkar 2018; De Rooij 2020).

All included studies used the same nucleoplasty intervention (Abrishamkar 2018; Birnbaum 2009; Cesaroni 2010; De Rooij 2020; Halim 2016; Nardi 2005). Three studies used as reference treatment conservative treatment (Nardi 2005; Birnbaum 2009; Cesaroni 2010) however different kinds of conservative treatment were used across the studies. Nardi 2005 used medical therapy consisting of anti-inflammatory drugs and cortisones for a period between 20 and 45 days and physical therapy included wearing of a Schanz collar for at least 30 days. Birnbaum 2009 used medical and physical therapy, however they did not explained what kind of forms of medical and physical therapy they used. Cesaroni 2010 used the following control interventions: transcutaneous electrical nerve stimulation, progressive neck mobilization (both active and passive) accompanied by a gradual reduction in collar usage, postural rehabilitation of the Mezieres technique, as well as analgesics and/or NSAIDs. One study used pulsed radiofrequency of the dorsal root ganglion, an acknowledged pain treatment modality for cervicogenic disc pain, as reference treatment (Halim 2016). One study used open discectomy, a surgical technique in which patients were operated in knee chest position under fenestration, as reference treatment (Abrishamkar 2018). And one study used anterior discectomy, a surgical technique in which the patient is positioned supine with the head in light extension, as reference treatment (De Rooij 2020).

Outcomes

Pain intensity of the arm and neck

Five studies reported pain intensity of the arm and/ or the neck using the visual analogue scale (VAS) (Abrishamkar 2018; Birnbaum 2009; Cesaroni 2010; De Rooij 2020; Halim 2016) De Rooij 2020 et al. estimated the means of the VAS of pain intensity of the arm and neck in a mixed model analyses. For this review we obtained the raw data of this RCT and used these for the analyses.

Neck-related functional status
Three studies reported neck-related functional status measured with NDI (Cesaroni 2010; De Rooij 2020; Halim 2016).

Recovery
One study reported the improved means of the Global Perceived Effect questionnaire (De Rooij 2020). For this review we obtained the raw study data to dichotomize these means into patients who have been recovered and not recovered. One study reported recovery measured with satisfaction of the intervention, however they did not describe how they measured it (Abrishamkar 2018). One study reported recovery measured by global perceived effect (Halim 2016), and one study reported subjective improvement of symptoms (complete resolution of symptoms, satisfactory amelioration of symptoms and the intervention did not change clinical status) (Nardi 2005).

Global health status
Two studies reported global health status (Cesaroni 2010; De Rooij 2020). For De Rooij 2020 et al. we obtained the raw data of this RCT and used these for the analyses.

Work-related disability
None of the included studies reported work-related disability.

Psycho-social outcomes
None of the included studies reported psycho-social outcomes.

Adverse effects
All studies reported on adverse effects (Abrishamkar 2018; Birnbaum 2009; Cesaroni 2010; De Rooij 2020; Halim 2016; Nardi 2005).

Timing of outcome assessments
All studies reported short-term follow-up (up to and including 3 months) (Abrishamkar 2018; Birnbaum 2009; Cesaroni 2010; De Rooij 2020; Halim 2016; Nardi 2005), 3 studies reported medium-term follow-up (more than 3 and less than 12 months) (Abrishamkar 2018; Birnbaum 2009; Cesaroni 2010; Abrishamkar 2018) and 3 studies reported long-term follow-up (1 year or longer) (Birnbaum 2009; Cesaroni 2010; De Rooij 2020).

Excluded studies
We excluded 8 studies because the study design was not a RCT or NRCT. Seven studies were case studies (Azzazi 2010; Bonaldi 2006; Cesaroni 2011; Li 2008; Sim 2011; Yan 2010; Ierardi 2020) and one study was a paper of a case study presented at a congress (Slipman 2003). We provide more details of excluded studies in the Characteristics of excluded studies Table 7.

Risk of bias in included studies

We have presented our 'Risk of bias' judgements separately for RCTs and NRCTs in the 'Risk of bias' tables (see Characteristics of included studies [ordered by study ID] and risk of bias for RCTs Table 5 and for NRCTs Table 6) and visualised for each study in the 'Risk of bias' summaries (see Figure 2; Figure 3). Our judgements about each 'Risk of bias' domain presented as percentages across all included studies are displayed in the 'Risk of bias' graphs (see Figure 4 and Figure 5).

Non-Randomised controlled trials

The ROBINS-I assessment process judges the RoB in seven domains resulting in an overall judgement of RoB corresponding to the highest level of risk displayed in any domain. In Table 6 the RoB of the two NRCTS are displayed within these seven domains. Assessment of risk of bias for the NRCTs (Birnbaum 2009 and Nardi 2005) resulted in a judgment of 'critical risk of bias' because these studies did not consider confounding (see Table 6). Furthermore, in the study of Nardi 2005 it was unclear how many patients did not complete follow up, it seems the report is only about the patients that completed the protocol. It is uncertain if there were dropouts or not. Birnbaum 2009 did not present dropouts in their study. We assessed the overall RoB to be critical for both NRCTs (Birnbaum 2009; Nardi 2005).

Table 25.3.c of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) recommends to not include studies with this level of bias in the synthesis, therefore we excluded these studies from the analysis.

Randomised controlled trials

Our 'Risk of bias' judgements using the Cochrane tool risk of bias tool for the four included RCTs are shown in Figure 2. Based on high risk of detection bias and attrition bias, we scored these four RCTs as 'high risk of bias' studies (Abrishamkar 2018; Cesaroni 2010; De Rooij 2020; Halim 2016).

Allocation (selection bias)

Four studies were RCTs of which two studies were judged as having unclear risk of bias because no information was available of allocation concealment (Cesaroni 2010; Abrishamkar 2018). Halim et al. (Halim 2016) also did not describe the method of allocation concealment (Halim 2016). However, we received additional information of the author, and we concluded they used an appropriate method of allocation concealment and judged this study as low risk of bias. De Rooij et al. (De Rooij 2020) had an independent observer who provided the trial coordinator with sealed envelopes containing the randomization assignments and was therefore judged as low risk of bias.

Blinding (performance bias and detection bias)
Three studies could not blind participants or care-providers, due to the fact that nucleoplasty treatment was compared to conservative treatment (Cesaroni 2010) or surgery (Abrishamkar 2018; De Rooij 2020). Risk of performance bias was unclear because there was no information on deviation from the intended interventions. Risk of outcome detection was assessed as high risk of bias, as all outcomes are patient-reported.

One study compared nucleoplasty treatment to pulse radio frequency of the dorsal root ganglion, which are both minimally invasive techniques. The protocol of this RCT reported that participants and outcome assessors were masked (Halim 2016). Additional information from the corresponding author revealed that the involved researcher (outcome assessor) was only being informed via the Case Report Form (CRF) whether the patient was assigned to group one or two, without knowing which group contains what type of treatment. By following this procedure as well patients as the outcome assessor were regarded blinded for the allocated treatment. This provided the possibility for blinded completion of the questionnaires during follow-up visits and blinded data-analysis. Therefore, this included study had a low risk of detection bias and performance bias (Halim 2016).

Incomplete outcome data (attrition bias)
Loss to follow was low and non-selective for three RCTs (Abrishamkar 2018; Cesaroni 2010; De Rooij 2020). The loss to follow-up varied from 2%-20%. Risk of attrition bias was low for these RCTs. Halim 2016 reported 15% dropouts in the nucleoplasty group and 29% in the pulsed radio frequency group. Reasons for drop-out were not provided, and we assessed risk of attrition bias high for this RCT.

Selective reporting (reporting bias)
Two studies were registered in a registry for clinical trials (De Rooij 2020; Halim 2016) and had no deviations from the protocol. Cesaroni 2010 did not have a protocol registered, but the pre-defined outcomes in the methods' section were reported in the results section. These three RCTs were assessed as low risk of reporting outcome bias. One RCT had no protocol and was inadequately reported (Abrishamkar 2018), resulting in an unclear risk of reporting outcome bias.

Other potential sources of bias
There were no other sources of bias identified.

Effects of interventions

See: Summary of findings table 1 for Nucleoplasty compared to conservative treatment, Summary of findings table 2 for Nucleoplasty compared to pulsed radio frequency and Summary of findings table 3 for Nucleoplasty compared to open discectomy.

Comparison 1 Nucleoplasty versus no treatment or placebo treatment

We did not find any RCT or NRCT on this comparison, therefore we did not create a summary of findings table for this comparison.

Comparison 2 Nucleoplasty versus conservative treatment

One RCT (Cesaroni 2010) with 120 participants and high risk of bias (lack of blinding), compared nucleoplasty (n=62) to an array of conservative treatment (n=58) in patients with symptomatic contained cervical disc herniations with a long-term follow-up time. The conservative treatment included transcutaneous electrical nerve stimulation (TENS), progressive neck mobilisation (both active and passive) accompanied by a gradual reduction in collar usage, postural rehabilitation of the Mezieres technique, as well as analgesics and/or NSAIDs. Outcomes were measured at 3 months (short-term follow-up), 6 months (medium-term follow-up) and 12 months (long-term follow-up).

Primary outcomes

Compared to conservative treatment, nucleoplasty may reduce **pain intensity** (VAS: 0 mm-100 mm scale) at long-term follow-up (clinically relevant mean difference (MD) of -29.28, 95% CI -36.40 to -22.16; Analysis 1.1). At short-term follow up nucleoplasty may reduce pain intensity slightly (MD -22.71, 95% confidence interval (CI) -30.10 to -15.32); Analysis 1.1). There was little to no difference in pain intensity at medium-term follow-up (MD -15.96, 95% CI -23.15 to -8.77; Analysis 1.1). However, these results did not meet the threshold for a clinically important difference.

Nucleoplasty may result in little to no difference in **neck-related functional status** (NDI: 0-50 scale, where lower scores indicate less disability) at short-term follow-up (MD -2.48, 95% CI -5.11 to 0.15; Analysis 1.2), medium-term follow-up (MD -0.50, 95% CI -3.20 to 2.20; Analysis 1.2) and long-term follow-up (MD -4.30, 95% CI -6.83 to -1.77; Analysis 1.2).

For **pain intensity** and **neck-related functional status** the certainty of the evidence was low; we downgraded the quality of the evidence for serious risk of bias and serious imprecision.

Recovery was not measured for this comparison.

Secondary outcomes
With regard to our secondary outcome global health status we decided to present the data of the items physical function and social function, because these two items approach the global health status the most. A higher score means a better self-reported health (scale of 0 = the worst health to 100 = ideal health).

Compared to conservative treatment, nucleoplasty may result in little to no difference on **global health status - physical function** at short-term (MD 1.48, 95% CI -1.65 to 4.61; Analysis 1.3), medium-term (MD 0.42, 95% CI -3.18 to 4.02; Analysis 1.3). Nucleoplasty may increase **global health status - physical function** at long-term follow-up (clinically relevant MD 5.37, 95% CI 1.30 to 9.44; Analysis 1.3).

Nucleoplasty may result in little to no difference on **global health status - social function** at short-term (MD -2.23, 95% CI -5.89 to 1.43; Analysis 1.4), medium-term follow-up (MD -5.54, 95% CI -1.28 to -9.80; Analysis 1.4) and long-term follow-up (MD 0.52, 95% CI -4.33 to 5.37; Analysis 1.4).

For **global health status** the quality of the evidence was low; we downgraded the certainty of the evidence for serious risk of bias and serious imprecision.

Work-related disability and **psycho-social outcomes** were not measured for this comparison.

We found very low-certainty evidence for the risk of **adverse effects** for nucleoplasty versus conservative treatment (Analysis 1.5). Cesaroni 2010 stated that they "did not observe significant clinical events beyond local-anaesthetic-related side effects", but the study authors did not report which side effects they observed. At 6-month follow-up, one patient in the cervical nucleoplasty group and one patient in the conservative treatment group underwent micro discectomy with fusion, however the study authors did not explain what the indication for this surgical treatment was. We downgraded the evidence by three levels, one for serious risk of bias and two for very serious imprecision.

Comparison 3 Nucleoplasty versus pulsed radio frequency of the dorsal root ganglion

One RCT of 34 participants (Halim 2016) and high risk of bias (attrition bias) compared nucleoplasty (n=17) to pulsed radio frequency of the dorsal root ganglion (n=17) with a short-term follow-up time of three months.

Primary outcomes
Compared to pulsed radio frequency, nucleoplasty may result in little to no difference on **pain intensity** (VAS: 0 mm-100 mm) (MD -7.9, 95% CI-29.45 to 13.65; Analysis 2.1),

neck-related functional status (NDI: 0-50 scale, where lower scores indicate less disability) (MD 0.30, 95% CI -6.97 to 7.57; Analysis 2.2) and **recovery** (MD -5.10, 95% CI -29.92 to 19.72; Analysis 2.3) at short-term follow-up.

Secondary outcomes
For this comparison there were no data on **global health status**, **work-related disability** and **psycho-social outcomes.**

With regard to **adverse effects**, Halim 2016 reported that there were no serious complications. There were minor side effects, these were transient and of mild severity for both groups. In the nucleoplasty group 3 patients experienced complications in the neck area, consisting of problems with swallowing. In the pulsed radio frequency of the dorsal root ganglion group 3 patients experienced complications mainly outside the neck region, such as headaches and muscle stiffness (RR 1.0, 95% CI 0.17 to 5.83; Analysis 2.4).

For the primary and the secondary outcomes the certainty of the evidence was very low; we downgraded the quality of the evidence for serious risk of bias and very serious imprecision (pain intensity, neck-related functional status, recovery and adverse effects). For recovery, we also downgraded for serious indirectness as recovery was measured as patient satisfaction.

Comparison 4 Nucleoplasty versus surgery
Two trials compared nucleoplasty with surgery. One trial (De Rooij 2020) with 48 participants and high risk of bias (lack of blinding) compared nucleoplasty (n=24) to anterior discectomy (n=24). Outcomes were measured at 3 months (short-term follow-up) and 12 months (long-term follow-up). The second trial (Abrishamkar 2018) with 70 participants and high risk of bias (lack of blinding) compared nucleoplasty (n=35) to open discectomy (n=35). Outcomes in this trial were measured at 3 and 6 months follow up (short-term and medium-term follow-up).

Primary outcomes
Compared to surgery, nucleoplasty may result in little to no difference in **arm pain intensity** (VAS: 0 mm-10 mm scale) at short-term (2 RCTs, no meta-analysis, MDs were -0.90 and 0.80; Analysis 3.1), medium-term (1 RCT, MD 0.70, 95% CI 0.36 to 1.04; Analysis 3.1) and long-term follow up (1 RCT, MD 0.70, 95% CI -0.84 to 2.24; Analysis 3.1). The results are very heterogyn and therefore we did not performed a meta-analysis.

For medium-term and long-term follow up we downgraded the certainty of evidence for arm pain intensity to low because of serious risk of bias and serious imprecision, and for short-term follow to very low because of serious risk of bias, imprecision and inconsistency.

Nucleoplasty may result in little to no difference in **neck pain intensity** (VAS: 0 mm-10 mm scale) at short-term (2 RCTs, MD 0.33, 95% CI -0.36 to 1.03; Analysis 3.2), medium-term (1 RCT, MD 0.40, 95% CI -0.12 to 0.92; Analysis 3.2) and long-term follow-up (1 RCT, MD 1.19, 95% CI -0.28 to 2.66; Analysis 3.2).

Nucleoplasty may result in little to no difference in **neck-related functional status** (NDI) at short-term (1 RCT, MD -0.69, 95% CI -12.63 to 11.25; Analysis 3.3) and medium-term (1 RCT, MD -0.22, 95% CI -12.31 to 11.87; Analysis 3.3).

For **neck pain intensity** and **neck-related functional status** the certainty of the evidence was low; we downgraded for serious risk of bias and serious imprecision.

The evidence is very uncertain about the effect of nucleoplasty compared to surgery on **recovery** 3, 6 and 12 months after treatment (1 RCT, RR 0.81, 95% CI 0.51 to 1.29; 1 RCT, RR=0.83, 95% CI 0.47 to 1.46 and 1 RCT, RR=0.71, 95% CI 0.44 to 1.14, respectively; Analysis 3.4). We downgraded the evidence by three levels for serious risk of bias, very serious imprecision and serious indirectness (recovery was measured as patient satisfaction).

Secondary outcomes

There was low-certainty evidence that compared to surgery, nucleoplasty may result in little to no difference on **global health status - physical function** at short-term follow-up (≤ 3 months) (1 RCT, MD -0.20, 95% CI -13.22 to 12.82; Analysis 3.5) and at medium-term-follow-up (≥ 3 months and ≤ 12 months) (1 RCT, MD 1.85, 95% CI -12.14 to 15.85; Analysis 3.5). We downgraded the evidence by two levels, one for serious risk of bias and one for serious imprecision.

We found low-certainty evidence that compared to surgery, nucleoplasty may result in little to no difference on **global health status - social function** at short-term follow-up (≤ 3 months) (1 RCT, MD 0.37, 95% CI -14.63 to 15.37; Analysis 3.6) and at medium-term follow-up (≥ 3 months and ≤ 12 months) MD -3.53, 95% CI -20.06 to 13.00; Analysis 3.6). We downgraded the evidence by two levels, one for serious risk of bias and one for serious imprecision.

Work-related disability and **psycho-social outcomes** were not measured for this comparison.

There was low-certainty evidence about the risk of **adverse effects** between the two treatments (Analysis 3.7). Abrishamkar 2018 (n=70, follow up 6 months) did not observe discitis, infection and haematoma in the surgery group. In this RCT (Abrishamkar 2018) one patient in the nucleoplasty group was operated again, however they did not explain why and at what follow-up time this patient was operated again. Furthermore, one

patient in the nucleoplasty group still suffered from cervical pain after 6 months and in the open discectomy group one patient suffered from arm pain 6 months after the operation. In the other RCT (De Rooij 2020) (n=48, follow up 12 months) 3 patients in the surgery group experienced adverse effect directly related to the operation. In the nucleoplasty group no adverse events occurred directly related to the procedure. We downgraded the evidence by one level for risk of bias and one level for serious imprecision.

Sensitivity analysis

We could not perform this sensitivity analysis because we had only one study for each outcome.

Discussion

Summary of main results

We found 6 eligible studies, four RCTs (Abrishamkar 2018; Cesaroni 2010; De Rooij 2020; Halim 2016) and two NRCTs (Birnbaum 2009; Nardi 2005). All outcomes were within the scope of this review (pain intensity, neck-related functional status, recovery, global health status and adverse effects), however work-related disability and psycho-social outcomes were missing. The two NRCTs studies had critical risk of bias and were not included in the analysis.

Compared to conservative treatment the data suggest that nucleoplasty may reduce pain intensity and may improve global health status - physical functioning at long-term follow-up, but not at shorter term. Both of these results reached clinical relevance. However, effect sizes were small and the certainty of evidence was low to very low, mostly because of risk of bias and imprecision.

The data of the other comparisons, i.e. nucleoplasty compared to pulsed radio frequency of the dorsal root ganglion and surgery, suggest that there is little to no difference available on the outcomes at all follow-up times. The effect sizes were small as well and the certainty of evidence was low, because of serious risk of bias and serious imprecision.

Overall completeness and applicability of evidence

Based upon the very low availability of trials and very limited treatment comparisons, i.e. the lack of a placebo treatment, the effectiveness of cervical nucleoplasty versus other comparison treatments for patients with cervical radicular pain due to a disc herniation is uncertain. We could not find published studies that described the effectiveness of nucleoplasty versus anterior and posterior decompression with non-fusion techniques; fusion techniques by plate, cage, autograft, allograft material, or artificial disc; or a combination.

Quality of the evidence

The high risk of bias and small sample sizes in the included studies led to the downgrading of the evidence (i.e. risk of bias and imprecision) for all treatment comparisons. As a result, there was mostly low- to very low certainty of evidence for the outcomes in the comparisons of interest of this review.

Due to the nature of the studied intervention different types of bias may have been introduced in the findings. In the RCTs there was a lack of blinding of participants, blinding of health care providers and blinding of outcome assessment. Also, five of the six included trials (Abrishamkar 2018; Birnbaum 2009; Cesaroni 2010; Halim 2016; Nardi 2005) did not perform an intention to treat analyses, however the loss of follow-up in these RCTs was low. In the NRCTs (Birnbaum 2009; Nardi 2005) there was a high risk of bias due to confounding, bias due to selection of participants and bias in classification of the intervention. We assessed the four RCTs as 'high risk of bias studies' (Abrishamkar 2018; Cesaroni 2010; Halim 2016; De Rooij 2020) and the NRCTs as 'critical risk studies' (Birnbaum 2009; Nardi 2005). Consequently, we can say that the included studies of this review were of low methodological quality.

Findings from the included studies on each primary and secondary outcomes and the corresponding certainty of evidence gradings are shown in the Summary of findings tables for the comparisons (Summary of findings table 1; Summary of findings table 2; Summary of findings table 3).

Potential biases in the review process

To minimise the risk of bias of the review, we followed the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions for searching, study selection, methodological appraisal, data collection and data analysis (Higgins 2011).

Limitations of this review include: (a) the lack of meta-analyses because we had only one to two trials in each comparison group, (b) lack of data, i.e. some studies did not clearly report their study results. Unfortunately, we did not receive from all corresponding authors additional information. More complete information might have resulted in a lower risk of bias of these studies.

Agreements and disagreements with other studies or reviews

This is the first Cochrane review that investigates whether cervical nucleoplasty improves clinical and functional outcomes compared to surgery, non-surgical interventions (pulsed radio frequency) and conservative treatment for patients with cervical radicular pain due to a disc herniation. There is one other systematic review (Wullems 2014) which have assessed the effect of nucleoplasty in patients with a (contained) cervical herniated disc, however they included two NRCTS (Nardi 2005 ; Birnbaum 2009) as RCTs. The authors of this systematic review concluded that nucleoplasty is a safe and

effective procedure and that the level of evidence for cervical nucleoplasty is moderate due to the small number of studies and the poor methodological quality of the RCTs (Wullems 2014). These findings are in line with our Cochrane review, but in contrast to Wullems 2014 we used the GRADE approach to assess the certainty of evidence of the trials and found low to very low-certainty of evidence of the included trials.

Authors' conclusion

Implications for practice

The evidence from this systematic review is uncertain regarding the effect of nucleoplasty on pain intensity in patients with cervical radicular pain due to a disc herniation. There is some evidence that nucleoplasty may reduce pain intensity and improve global health status-physical function at long-term follow-up, but not at shorter term. However, the certainty of this evidence is low.

Implications for research

There is a need for additional large, well-designed RCTs before we can describe the value of nucleoplasty for clinical practice in patients with cervical radicular pain due to a disc herniation.

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Contributions of authors

W. Bramer performed the electronic searches in the databases. J.D. de Rooij and B.S. Harhangi screened the titles and abstracts of all studies retrieved by the searches to identify those meeting the inclusion criteria. In case of disagreement, they consulted J.G. Groeneweg. J.D. de Rooij and M.L.Langendam assessed the risks of bias of all included studies. In case of disagreement, they consulted A. P. Verhagen. J.D. de Rooij and M.L Langendam judged the quality of evidence, following the GRADE guidelines. J.D. de Rooij and M.L. Langendam drafted the final manuscript. All authors participated in the interpretation of the results, reading and approving the final manuscript.

Declaration of interest

J.D.de Rooij, M.L. Langendam, B.S. Harhangi, J.G, Groeneweg, M.G Fehlings, A.P. Verhagen have no known conflicts of interest. J.P. Huygen received grants/research support and educational grants from ABBOTT, Saluda and Boston Scientific. These are not related to the submitted work.

Differences between protocol and review

- We added an extra comparison: nucleoplasty versus minimally-invasive interventions (pulsed radio frequency of the dorsal root ganglion).
- Instead of using the Downs and Black checklist, we used the Risk Of Bias In Non-randomized Studies - of Interventions (ROBIN-I) tool to assess the risk of bias for the Non-randomised controlled trials (NRCTs).
- There is no universally accepted definition of cervical radicular pain (CRP) due to a disc herniation. CRP, cervical radiculopathy or cervical radicular syndrome have often been used interchangeably in the literature. To avoid confusion we prefer to change the title of this systematic review from 'Nucleoplasty for cervical radicular pain or cervical radiculopathy, or both due to a disc herniation' into 'Nucleoplasty for cervical radicular pain due to a disc herniation'.

APPENDICES

Appendix 1 Search strategies

EMBASE

Last searched October 5th 2021

(((neck/exp OR 'neck pain'/exp OR arm/exp OR 'cervical spine'/exp OR shoulder/exp OR 'shoulder pain'/exp OR (neck OR arm OR (upper NEAR/3 (extremit* OR limb*)) OR shoulder* OR cervic* OR cervix* OR c1 OR c2 OR c3 OR c4 OR c5 OR c6 OR c7)) AND ('radicular pain'/exp OR radiculopathy/exp OR radiculitis/exp OR 'spinal cord compression'/exp OR 'Spinal Root'/de OR 'intervertebral disk hernia'/de OR (radiculalg* OR radiculopath* OR polyradiculopath* OR Polyradiculoneuropath* OR (Compress* NEAR/3 Myelopath*) OR radiculitis OR ((radicul* OR 'nerve root' OR 'nerve roots') NEAR/3 (pain* OR neuralg*)) OR ((Spinal OR nerve OR ventral OR dorsal) NEAR/3 (Root* OR cord*)) OR (vertebral NEAR/3 compress*) OR ((disc OR discs OR discogen* OR disk OR disks OR vertebr* OR intervertebr*) NEAR/6 (herni* OR pain* OR protrus* OR displace*)))))) OR ('cervicobrachial neuralgia'/exp OR (((cervicobrach* OR 'cervico-brachial' OR 'cervical brachial') NEAR/3 neuralg*) OR (('arm neck shoulder' OR 'neck shoulder arm' OR 'shoulder arm neck' OR cervical*) NEXT/1 syndrom*) OR (cervicobrach* NEAR/3 (disease* OR pain* OR syndrome*)) OR cervicobrachialg*))) AND ((((Plasma OR laser OR thermal OR needle OR percutan*) NEAR/6 (decompression OR compression OR discectom* OR removal)) OR coblation OR Nucleoplast* OR pldd))

MEDLINE

Last searched October 5th 2021

(((neck/ OR Neck Muscles/ OR exp Cervical Vertebrae/ OR neck pain/ OR exp arm/ OR exp shoulder/ OR Shoulder Pain/ OR Shoulder Joint/ OR (neck OR arm OR (upper ADJ3 (extremit* OR limb*)) OR shoulder* OR cervic* OR cervix* OR c1 OR c2 OR c3 OR c4 OR c5 OR c6 OR c7)) AND (radiculopathy/ OR Polyradiculoneuropathy/ OR spinal cord compression/ OR exp Spinal Nerve Roots/ OR Intervertebral Disc Displacement/ OR (radiculalg* OR radiculopath* OR polyradiculopath* OR Polyradiculoneuropath* OR (Compress* ADJ3 Myelopath*) OR radiculitis OR ((radicul* OR nerve root OR nerve roots) ADJ3 (pain* OR neuralg*)) OR ((Spinal OR nerve OR ventral OR dorsal) ADJ3 (Root* OR cord*)) OR (vertebral ADJ3 compress*) OR ((disc OR discs OR discogen* OR disk OR disks OR vertebr* OR intervertebr*) ADJ6 (herni* OR pain* OR protrus* OR displace*))))) OR (Brachial Plexus Neuritis/ OR (((cervicobrach* OR cervico-brachial OR cervical brachial) ADJ3 neuralg*) OR ((arm neck shoulder OR neck shoulder arm OR shoulder arm neck OR cervical*) ADJ syndrom*) OR (cervicobrach* ADJ3 (disease* OR pain* OR syndrome*)) OR cervicobrachialg*))) AND ((((Plasma OR laser OR thermal

OR needle OR percutan*) ADJ6 (decompression OR compression OR discectom* OR removal)) OR coblation OR Nucleoplast* OR pldd))

CENTRAL

Last searched October 5th 2021 using CRS Web

((((neck OR arm OR (upper NEAR3 (extremit* OR limb*)) OR shoulder* OR cervic* OR cervix* OR c1 OR c2 OR c3 OR c4 OR c5 OR c6 OR c7)) AND ((radiculalg* OR radiculopath* OR polyradiculopath* OR Polyradiculoneuropath* OR (Compress* NEAR3 Myelopath*) OR radiculitis OR ((radicul* OR 'nerve root' OR 'nerve roots') NEAR3 (pain* OR neuralg*)) OR ((Spinal OR nerve OR ventral OR dorsal) NEAR3 (Root* OR cord*)) OR (vertebral NEAR3 compress*) OR ((disc OR discs OR discogen* OR disk OR disks OR vertebr* OR intervertebr*) NEAR (herni* OR pain* OR protrus* OR displace*))))) OR ((((cervicobrach* OR 'cervico-brachial' OR 'cervical brachial') NEAR3 neuralg*) OR (('arm neck shoulder' OR 'neck shoulder arm' OR 'shoulder arm neck' OR cervical*) NEXT syndrom*) OR (cervicobrach* NEAR3 (disease* OR pain* OR syndrome*)) OR cervicobrachialg*))) AND ((((Plasma OR laser OR thermal OR needle OR percutan*) NEAR (decompression OR compression OR discectom* OR removal)) OR coblation OR Nucleoplast* OR pldd)) AND CENTRAL:TARGET

Web of Science

Last searched October 5th 2021

TS=(((((neck OR arm OR (upper NEAR/3 (extremit* OR limb*)) OR shoulder* OR cervic* OR cervix* OR c1 OR c2 OR c3 OR c4 OR c5 OR c6 OR c7)) AND ((radiculalg* OR radiculopath* OR polyradiculopath* OR Polyradiculoneuropath* OR (Compress* NEAR/3 Myelopath*) OR radiculitis OR ((radicul* OR "nerve root" OR "nerve roots") NEAR/3 (pain* OR neuralg*)) OR ((Spinal OR nerve OR ventral OR dorsal) NEAR/3 (Root* OR cord*)) OR (vertebral NEAR/3 compress*) OR ((disc OR discs OR discogen* OR disk OR disks OR vertebr* OR intervertebr*) NEAR/6 (herni* OR pain* OR protrus* OR displace*))))) OR ((((cervicobrach* OR "cervico-brachial" OR "cervical brachial") NEAR/3 neuralg*) OR (("arm neck shoulder" OR "neck shoulder arm" OR "shoulder arm neck" OR cervical*) NEAR/1 syndrom*) OR (cervicobrach* NEAR/3 (disease* OR pain* OR syndrome*)) OR cervicobrachialg*))) AND ((((Plasma OR laser OR thermal OR needle OR percutan*) NEAR/6 (decompression OR compression OR discectom* OR removal)) OR coblation OR Nucleoplast* OR pldd)))

SCOPUS

Last searched October 5th 2021

TITLE-ABS-KEY(((((neck OR arm OR (upper W/3 (extremit* OR limb*)) OR shoulder* OR cervic* OR cervix* OR c1 OR c2 OR c3 OR c4 OR c5 OR c6 OR c7)) AND ((radiculalg*

OR radiculopath* OR polyradiculopath* OR Polyradiculoneuropath* OR (Compress* W/3 Myelopath*) OR radiculitis OR ((radicul* OR "nerve root" OR "nerve roots") W/3 (pain* OR neuralg*)) OR ((Spinal OR nerve OR ventral OR dorsal) W/3 (Root* OR cord*)) OR (vertebral W/3 compress*) OR ((disc OR discs OR discogen* OR disk OR disks OR vertebr* OR intervertebr*) W/6 (herni* OR pain* OR protrus* OR displace*))))) OR ((((cervicobrach* OR "cervico-brachial" OR "cervical brachial") W/3 neuralg*) OR (("arm neck shoulder" OR "neck shoulder arm" OR "shoulder arm neck" OR cervical*) W/1 syndrom*) OR (cervicobrach* W/3 (disease* OR pain* OR syndrome*)) OR cervicobrachialg*))) AND ((((Plasma OR laser OR thermal OR needle OR percutan*) W/6 (decompression OR compression OR discectom* OR removal)) OR coblation OR Nucleoplast* OR pldd)))

CINAHL

Last searched October 5th 2021

(((MH neck+ OR MH "Neck Muscles+" OR MH "Cervical Vertebrae+" OR MH "neck pain+" OR MH arm+ OR MH shoulder+ OR MH "Shoulder Pain+" OR MH "Shoulder Joint+" OR (neck OR arm OR (upper N3 (extremit* OR limb*)) OR shoulder* OR cervic* OR cervix* OR c1 OR c2 OR c3 OR c4 OR c5 OR c6 OR c7)) AND (MH radiculopathy+ OR MH Polyradiculoneuritis+ OR MH "spinal cord compression+" OR MH "Spinal Nerve Roots+" OR MH "Intervertebral Disc Displacement+" OR (radiculalg* OR radiculopath* OR polyradiculopath* OR Polyradiculoneuropath* OR (Compress* N3 Myelopath*) OR radiculitis OR ((radicul* OR nerve root OR nerve roots) N3 (pain* OR neuralg*)) OR ((Spinal OR nerve OR ventral OR dorsal) N3 (Root* OR cord*)) OR (vertebral N3 compress*) OR ((disc OR discs OR discogen* OR disk OR disks OR vertebr* OR intervertebr*) N6 (herni* OR pain* OR protrus* OR displace*))))) OR (MH "Brachial Plexus Neuritis+" OR (((cervicobrach* OR cervico-brachial OR cervical brachial) N3 neuralg*) OR (("arm neck shoulder" OR "neck shoulder arm" OR "shoulder arm neck" OR cervical*) n1 syndrom*) OR (cervicobrach* N3 (disease* OR pain* OR syndrome*)) OR cervicobrachialg*))) AND ((((Plasma OR laser OR thermal OR needle OR percutan*) N6 (decompression OR compression OR discectom* OR removal)) OR coblation OR Nucleoplast* OR pldd))

PubMed

Last searched October 5th 2021

(((neck[mh] OR Neck Muscles[mh] OR Cervical Vertebrae[mh] OR neck pain[mh] OR arm[mh] OR shoulder[mh] OR Shoulder Pain[mh] OR Shoulder Joint[mh] OR (neck OR arm OR (upper AND (extremit*[tiab] OR limb*[tiab])) OR shoulder*[tiab] OR cervic*[tiab] OR cervix*[tiab] OR c1 OR c2 OR c3 OR c4 OR c5 OR c6 OR c7)) AND (radiculopathy[mh] OR Polyradiculoneuropathy[mh] OR spinal cord compression[mh] OR Spinal Nerve Roots[mh] OR Intervertebral Disc Displacement[mh] OR (radiculalg*[tiab] OR

radiculopath*[tiab] OR polyradiculopath*[tiab] OR Polyradiculoneuropath*[tiab] OR (Compress*[tiab] AND Myelopath*[tiab]) OR radiculitis OR ((radicul*[tiab] OR nerve root OR nerve roots) AND (pain*[tiab] OR neuralg*[tiab])) OR ((Spinal OR nerve OR ventral OR dorsal) AND (Root*[tiab] OR cord*[tiab])) OR (vertebral AND compress*[tiab]) OR ((disc OR discs OR discogen*[tiab] OR disk OR disks OR vertebr*[tiab] OR intervertebr*[tiab]) AND (herni*[tiab] OR pain*[tiab] OR protrus*[tiab] OR displace*[tiab])))) OR (Brachial Plexus Neuritis[mh] OR (((cervicobrach*[tiab] OR cervico-brachial OR cervical brachial) AND neuralg*[tiab]) OR arm neck shoulder syndrom*[tiab] OR neck shoulder arm syndrom*[tiab] OR shoulder arm neck syndrom*[tiab] OR cervical syndrom*[tiab] OR (cervicobrach*[tiab] AND (disease*[tiab] OR pain*[tiab] OR syndrome*[tiab])) OR cervicobrachialg*[tiab]))) AND ((((Plasma OR laser OR thermal OR needle OR percutan*[tiab]) AND (decompression OR compression OR discectom*[tiab] OR removal)) OR coblation OR Nucleoplast*[tiab] OR pldd)) AND publisher[sb]

ClinicalTrials.gov
Last searched October 5th 2021

(neck OR cervical) AND (radiculopathy OR "radiculair pain") AND percutaneous

Google Scholar
Last searched October 5th 2021

Neck|cervical|cervicobrachial|"cervico-brachial"adiculalgia|radiculopathy|polyradiculopathy|Compression|hernia|radiculitis|"Spinal|nerve Root|cord" "Plasma|laser|thermal|needle|percutaneous * decompression|compression|discectomy"|Nucleoplast|pldd

Physiotherapy Evidence Database (PEDro)
Last searched October 5th 2021

Abstract and title: percutaneous

Problem: pain

Body part: head or neck

WHO ICTRP
Last searched October 5th 2021

neck AND radiculopathy AND percutaneous OR cervical AND radiculopathy AND percutaneous OR neck AND "radicular pain" AND percutaneous OR cervical AND "radicular pain" AND percutaneous

Appendix 2 The GRADE approach to evidence synthesis

The quality of evidence will be categorised as follows:

- High (●●●●): further research is very unlikely to change the confidence in the estimate of effect.
- Moderate (●●●○): further research is likely to have an important impact in the confidence in the estimate of effect.
- Low (●●○○): further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
- Very low (●○○○): any estimate of effect is very uncertain.

The evidence available to answer each sub-question will be graded on the domains in the following manner:

1. Study design
We included randomized controlled trials and controlled clinical trials in this review

2. Risk of bias
We downgraded the quality of evidence by one level when 25% of the participants were form studies judged as high risk of bias (i.e. one of the following criteria judged as having 'high'or 'unclear' risk of bias: random allocation, allocation concealment, blinding procedures, and adequate follow-up).

Limitations in the study design and implementation may bias the estimates of the treatment effect. Our confidence in the estimate of the effect and in the following recommendation decreases if studies suffer from major limitations. We will examine all studies on five types of biases:

a) Selection (random sequence generation, allocation concealment, group similarities at baseline);

We scored this domain as low risk of bias if random sequence generation and allocation concealment were judged as having low risk.

b) Performance (blinding of participants, blinding of healthcare providers);

We scored this domain as low risk of bias if blinding of participants and healthcare providers were judged as having low risk

c) Attrition (dropouts and intention-to-treat analysis);

We scored this domain as low risk of bias if blinding of outcomes was judged as having low risk

d) Detection (blinding of the outcome assessors and timing of outcome assessment);

We scored this domain as low risk of bias if blinding of outcomes was judged as having low risk.

e) Reporting bias (selective reporting);

We will score this item as low risk of bias if it is defined as having low risk.

We considered the studies as having low risk of bias, if we judged four of five bias as having low risk of bias.

3. Inconsistency

Inconsistency refers to an unexplained heterogeneity of results. Widely differing estimates of the **treatment effect** (i.e. heterogeneity or variability in results) across studies suggest true differences in underlying treatment effect. Inconsistency may arise from differences in: **populations** (e.g. drugs may have larger relative effects in sicker populations), **interventions** (e.g. larger effects with higher drug doses), or **outcomes** (e.g. diminishing treatment effect with time). The quality of evidence will be downgraded as follows:

- by one level: when the heterogeneity or variability in results is large (for example: I^2 above 75%)
- by two levels: when the heterogeneity or variability in results is large AND there was inconsistency arising from populations, interventions or outcomes.

4. Indirectness

Indirect population, intervention, comparator, or outcome - the question being addressed in this systematic review is different from the available evidence regarding the population, intervention, comparator, or an outcome in the included randomised trial.

The quality of evidence will be downgraded as follows:

- by one level: when there is indirectness in only one area
- by two levels: when there is indirectness in two or more areas

5. Imprecision

Results are imprecise when studies include relatively few patients and few events and thus have wide confidence intervals around the estimate of the effect. In this case we judge the quality of the evidence lower than it otherwise would be because of consequent uncertainty in the results. Each outcome is considered separately.

For dichotomous outcomes

We will consider imprecision for either of the following two reasons:

a) There is only one study. When there is more than one study, the total number of events is less than 300 (a threshold rule-of-thumb value) (Mueller 2007).
b) 95% confidence interval around the pooled or best estimate of effect includes both i no effect and ii appreciable benefit or appreciable harm. The threshold for 'appreciable benefit' or 'appreciable harm' is a relative risk reduction (RRR) or relative risk increase (RRI) greater than 25%.

The quality of the evidence will be downgraded as follows:

- by one level: when there is imprecision due to (a) or (b)
- by two levels: when there is imprecision due to (a) and (b)

For continuous outcomes

We will consider imprecision for either of the following two reasons:

a). When there is more than one study, total population size is less than 400 (a threshold rule-of-thumb value; using the usual α and β, and an effect size of 0.2 SD, representing a small effect)
b) 95% confidence interval includes no effect and the upper or lower confidence limit crosses an effect size (standardised mean difference) of 0.5 in either direction.

The quality of the evidence will be downgraded as follows:

- by one level: when there is imprecision due to (a) or (b)
- by two levels: when there is imprecision due to (a) and (b)

6. Publication bias

Publication bias is a systematic underestimate or overestimate of the underlying beneficial or harmful effect due to the selective publication of studies. The quality of evidence will be downgraded as follows:

- by one level: when the funnel plot suggests publication bias

REFERENCES

References to studies included in this review

Saeid Abrishamkar, Sohrab Salimi . Comparison the Postoperation results of Discectomy With Nucleoplasty in Single Cervical Disc Herniation. Advanced Biomedical Research 2018 Feb 16;7(29):1-5.

Birnbaum K. Percutaneous cervical disc decompression. Surgical and Radiologic Anatomy: SRA 2009;31(5):379-87.

Alessandro Cesaroni, Pier Vittorio Nardi. Plasma Disc Decompression for Contained Cervical Disc Herniation: A Randomized, Controlled Trial. European spine journal 2010 March;19(3):477-486.

Percutaneous plasma discectomy study. ISRCTN registry.

Judith de Rooij, Biswadjiet Harhangi, Hans Aukes, George Groeneweg, Dirk Stronks and Frank Huygen. The Effect of Percutaneous Nucleoplasty vs Anterior Discectomy in Patients with Cervical Radicular Pain due to a Single-Level Contained Soft-Disc Herniation: A Randomized Controlled Trial. Pain Physician November/December 2020;23(6):533-564.

Halim W, van der Weegen W, Lim T, Wullems JA, Vissers KC. Percutaneous Cervical Nucleoplasty vs. Pulsed Radio Frequency of the Dorsal Root Ganglion in Patients with Contained cervical Disk Herniation; A Prospective, Randomized Controlled Trial. Pain Practice 2016;17:729-737.

Willy Halim, Walter van der Weegen . Percutaneous Cervical Nucleoplasty vs. Pulsed Radio Frequency of the Dorsal Root Ganglion in Patients With Contained Cervical Disk Herniation; A Prospective, Randomized Controlled Trial. Pain practice 2017 July;17(6):729-737.

P V Nardi, D Cabezas, A Cesaroni. Percutaneous cervical nucleoplasty using coblation technology. Clinical results in fifty consecutive cases. Acta neurochirurgica. Supplement 2005;92:73-8.

References to studies excluded from this review

Azzazi A, Elhawary Y. Cervical nucleoplasty using coblation technology; clinical outcome. Neurosurgery quarterly 2010;20:146–150.

Bonaldi G. Baruzzi F, Facchinetti A, Fachinetti P, Lunghi S. Plasma Radio-Frequency–Based Diskectomy for Treatment of Cervical Herniated Nucleus Pulposus: Feasibility, Safety, and Preliminary Clinical results. AJNR Am J Neuroradiol 2006;27:2104–2111.

Cesaroni A, Nardi PV. Plasma-mediated disc decompression for contained cervical disc herniation: results through 5 years.. Acta neurochirurgica. Supplement 2011;108:113-116.

Anna Maria Ierardi , Aldo Carnevale . Percutaneous Cervical Discectomy: Retrospective Comparison of Two Different Techniques. La Radiologia medica 2020 Juni;125(6):569-577.

Li J, Yan DL, Zhang ZH.. Percutaneous cervicalnucleoplasty in the treatment of cervical disc herniation [European Spine Journal]. European Spine Journal 2008;17:1664–1669.

Sim SE, Ko ES, Kim DK, Kim HK, Kim YC, Shin HY. The results of cervical nucleoplasty in patients with cervicaldisc disorder: a retrospective clinical study of 22 patients.. The Korean journal of pain 2011;24:36-43.

Slipman C, Bhagia S, Frey M, el Abd O, Richards J, Chou L, Lenrow D. Nuceloplasty procedure for Cervical Radicular Pain-Initial Case Series. Paper presented at the 2nd World Congress of the InternationalSociety of Physical and Rehabilitation Medicine May18–22, Prague, Czech Republic.

Yan D, Li J, Zhu H, Zhang Z, Duan L. Percutaneouscervical nucleoplasty and percutaneous cervical discectomytreatments of the contained cervical disc herniation. Archives of orthopaedic and trauma surgery 2010;130:1371-1376.

Additional references

Leah Y. Carreon, Steven D. Glassman, Mitchell J. Campbell, Paul A. Anderson. Neck Disability Index, short form-36 physical component summary, and pain scales for neck and arm pain: the minimum clinically important difference and substantial clinical benefit after cervical spine fusion. The Spine Journal 2010;10:469–474.

Chen YC, Lee SH, Chen D. Intradiscal pressure study of percutaneous disc decompression with nucleoplasty in human cadavers. Spine (Phila Pa 1976) 2003;28(7):661-5.

de Bruin AF, Diederiks JP, de Witte LP, Stevens FC, Philipsen H. The development of a short generic version of the Sickness Impact Profile. Journal of Clinical Epidemiology 1994;47(4):407-18.

Dillin W, Booth R, Cuckler J, Balderston R, Simeone F, Rothman R. Cervical radiculopathy. A review. Spine (Philadelphia, Pa. : 1986) 1986;11(10):988-91.

Furlan AD, Malmivaara A, Chou R, Maher CG, Deyo RA, Schoene M, Bronfort G, van Tulder MW; Editorial Board of the Cochrane Back, Neck Group.. 2015 Updated Method Guideline for Systematic Reviews in the Cochrane Back and Neck Group.. Spine 2015;Nov;40(21):1660-73.

Gebremariam L, Koes BW, Peul WC, Huisstede BM. Evaluation of treatment effectiveness for the herniated cervical disc: a systematic review. Spine (Phila Pa 1976) 2012;37(2):E109-18.

Gerges FJ, Lipsitz SR, Nedeljkovic SS. A systematic review on the effectiveness of the Nucleoplasty procedure for discogenic pain. Pain Physician 2010;13(2):117-32.

GRADEpro GDT [Computer program]. GRADE Working Group, McMaster University. Hamilton (ON): GRADE Working Group, McMaster University, 2015, Version accessed 15 May 2017.

Gordon H. Guyatt, Andrew D. Oxman, Victor Montori, Gunn Vist, Regina Kunz, Jan Brozek, Pablo Alonso-Coello, Ben Djulbegovic, David Atkins, Yngve Falck-Ytter, John W. Williams Jr., Joerg Meerpohl, Susan L. Norris, Elie A. Akl, Holger J. Schünemann. GRADE guidelines: 5. Rating the quality of evidence—publication bias. Journal of Clinical Epidemiology December 2011;64(12):1277-1282.

Halim W, Wullems JA, Lim T, Aukes HA, van der Weegen W, Vissers KC, et al. The long-term efficacy and safety of percutaneous cervical nucleoplasty in patients with a contained herniated disk. Pain Practice 2013;13(5):364-71.

Higgins JPT, Green S, (editors). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.. Cochrane, 2011.

Jacobs WC, Arts MP, van Tulder MW, Rubinstein SM, van Middelkoop M, Ostelo RW, et al. Surgical techniques for sciatica due to herniated disc, a systematic review. European Spine Journal 2012;21(11):2232-51.

Kuijper B, Tans JT, Beelen A, Nollet F, de Visser M. Cervical collar or physiotherapy versus wait and see policy for recent onset cervical radiculopathy: randomised trial. BMJ Oct 7 2009;339:b3883.

Jacques Simon Lee, Elisabeth Hobden, Ian G Stiell, George A Wells. Clinically Important Change in the Visual Analog Scale after Adequate Pain Control. Academic Emergency Medicine 2003;10:1128-30.

Lees F, Turner JW. Natural history and prognosis of cervical spondylosis. British Medical Journal Dec 28 1963;2(5373):1607-10.

Lefebvre C, Glanville J, Briscoe S, Littlewood A, Marshall C, Metzendorf M-I, Noel-Storr A, Rader T, Shokraneh F, Thomas J, Wieland LS. Chapter 4: Searching for and selecting studies. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). In: Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated July 2019). Cochrane 2019, Available from www.training.cochrane.org/handbook.

Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J, Moher D.. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration.. British Medical Journal 2009 Jul 21;339:b2700.

Mueller PS, Montori VM, Bassler D, Koenig BA, Guyatt GH. Ethical issues in stopping randomized trials early because of apparent benefit. Ideas and Opnions 2007;146:878-82.

Nikolaidis I, Fouyas IP, Sandercock PA, Statham PF. Surgery for cervical radiculopathy or myelopathy. Cochrane Database of Systematic Reviews 2010, Issue 1. Art. No.: CD001466. DOI: 10.1002/14651858.CD001466.

Raymond W.J.G. Ostelo, Henrica C.W. de Vet. Clinically important outcomes in low back pain. Best Practice & Research Clinical Rheumatology 2005;19:593–607.

Radhakrishnan K, Litchy WJ, O'Fallon WM, Kurland LT. Epidemiology of cervical radiculopathy. A population-based study from Rochester, Minnesota, 1976 through 1990. Brain 1994;117(Pt 2):325-35.

Salemi G, Savettieri G, Meneghini F, Di Benedetto ME, Ragonese P, Morgante L, et al. Prevalence of cervical spondylotic radiculopathy: a door-to-door survey in a Sicilian municipality. Acta Neurologica Scandinavica 1996;93(2-3):184-8.

Schoenfeld AJ, George AA, Bader JO, Caram PM Jr. Incidence and epidemiology of cervical radiculopathy in the United States military: 2000 to 2009. Journal of Spinal Disorders & Techniques 2012;25(1):17-22.

Sim SE, Ko ES, Kim DK, Kim HK, Kim YC, Shin HY. The results of cervical nucleoplasty in patients with cervical disc disorder: a retrospective clinical study of 22 patients. Korean Journal of Pain 2011;24(1):36-43.

Sriwatanakul K, Kelvie W, Lasagna L, Calimlim JF, Weis OF, Mehta G. Studies with different types of visual analog scales for measurement of pain. Clinical Pharmacology &Therapeutics 1983;34(2):234-9.

Sterne JAC, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, Henry D, Altman DG, Ansari MT, Boutron I, Carpenter JR, Chan AW, Churchill R, Deeks JJ, Hróbjartsson A, Kirkham J, Jüni P, Loke YK, Pigott TD, Ramsay CR, Regidor D, Rothstein HR, Sandhu L, Santaguida PL, Schünemann HJ, Shea B, Shrier I, Tugwell P, Turner L, Valentine JC, Waddington H, Waters E, Wells GA, Whiting PF, Higgins JPT. ROBINS-I: a tool for assessing risk of bias in non-randomized studies of interventions.. BMJ 2016;355:i4919.

Thoomes EJ, Scholten-Peeters W, Koes B, Falla D, Verhagen AP.. The Effectiveness of Conservative Treatment for Patients With Cervical Radiculopathy: A Systematic Review. Clinincal Journal of Pain. 2013;29(12):1073-86.

van Middelkoop M, Rubinstein SM, Ostelo R, van Tulder MW, Peul W, Koes BW, et al. Surgery versus conservative care for neck pain: a systematic review. European Spine Journal 2013;22(1):87-95.

Veeravagu A, Cole T, Jiang B, Ratliff JK. Revision rates and complication incidence in single- and multilevel anterior cervical discectomy and fusion procedures: an administrative database study. Spine Journal 2014;14(7):1125-3.

Vernon H. The Neck Disability Index: state-of-the-art, 1991-2008. Journal of Manipulative and Physiological Therapeutics 2008;31(7):491-502.

Von Korff M, Jensen MP, Karoly P. Assessing global pain severity by self-report in clinical and health services research. Spine (Phila Pa 1976) 2000 Dec 5;15;25(24);:3140-51..

Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Medical Care 1992;30(6):473-83.

Williams A. EuroQol--a new facility for the measurement of health-related quality of life. The EuroQol Group. Health Policy 1990;16(3):199-208.

Wullems JA, Halim W, van der Weegen W. Current evidence of percutaneous nucleoplasty for the cervical herniated disk: a systematic review. Pain Practice 2014;14(6):559-69.

ADDITIONAL TABLES

Table 1 Sources of risk of bias

Bias domain	Source of bias	Possible answers
Selection	(1) Was the method of randomization adequate?	Yes/No/ Unsure
Selection	(2) Was the treatment allocation concealed?	Yes/No/ Unsure
Performance	(3) Was the patient blinded to the intervention?	Yes/No/ Unsure
Performance	(4) Was the care provider blinded to the intervention?	Yes/No/ Unsure
Detection	(5) Was the outcome assessor blinded to the intervention?	Yes/No/ Unsure
Attrition	(6) Was the drop-out rate described and acceptable?	Yes/No/ Unsure
Attrition	(7) Were all randomized participants analysed in the group to which they were allocated?	Yes/No/ Unsure
Reporting	(8) Are reports of the study free of suggestion of selective outcome reporting?	Yes/No/ Unsure
Selection	(9) Were the groups similar at baseline regarding the most important prognostic indicators?	Yes/No/ Unsure
Performance	(10) Were co interventions avoided or similar?	Yes/No/ Unsure
Performance	(11) Was the compliance acceptable in all groups?	Yes/No/ Unsure
Detection	(12) Was the timing of the outcome assessment similar in all groups?	Yes/No/ Unsure
Other	(13) Are other sources of potential bias unlikely?	Yes/No/ Unsure

Footnotes
Higgins 2011

Table 2 Criteria for a judgment of "Yes" for the sources of risk of bias

1	A random (unpredictable) assignment sequence. Examples of adequate methods are coin toss (for studies with 2 groups), rolling a dice (for studies with 2 or more groups), drawing of balls of different colours, drawing of ballots with the study group labels from a dark bag, computer-generated random sequence, preordered sealed envelopes, sequentially-ordered vials, telephone call to a central office, and preordered list of treatment assignments. Examples of inadequate methods are: alternation, birthdate, social insurance/security number, date in which they are invited to participate in the study, and hospital registration number.
2	Assignment generated by an independent person not responsible for determining the eligibility of the participants. This person has no information about the persons included in the trial and has no influence on the assignment sequence or on the decision about eligibility of the participant.
3	Index and control groups are indistinguishable for the participants or if the success of blinding was tested among the participants and it was successful.
4	Index and control groups are indistinguishable for the care providers or if the success of blinding was tested among the care providers and it was successful.
5	Adequacy of blinding should be assessed for each primary outcome separately. This item should be scored "yes" if the success of blinding was tested among the outcome assessors and it was successful or: -for patient-reported outcomes in which the patient is the outcome assessor (e.g., pain, disability): the blinding procedure is adequate for outcome assessors if participant blinding is scored "yes" -for outcome criteria assessed during scheduled visit and that supposes a contact between participants and outcome assessors (e.g., clinical examination): the blinding procedure is adequate if participants are blinded, and the treatment or adverse effects of the treatment cannot be noticed during clinical examination -for outcome criteria that do not suppose a contact with participants (e.g., radiography, magnetic resonance imaging): the blinding procedure is adequate if the treatment or adverse effects of the treatment cannot be noticed when assessing the main outcome -for outcome criteria that are clinical or therapeutic events that will be determined by the interaction between participants and care providers (e.g., co interventions, hospitalisation length, treatment failure), in which the care provider is the outcome assessor: the blinding procedure is adequate for outcome assessors if item "4" (caregivers) is scored "yes" -for outcome criteria that are assessed from data of the medical forms: the blinding procedure is adequate if the treatment or adverse effects of the treatment cannot be noticed on the extracted data
6	The number of participants who were included in the study but did not complete the observation period or were not included in the analysis must be described and reasons given. If the percentage of withdrawals and drop-outs does not exceed 20% for short-term follow-up and 30% for long-term follow-up and does not lead to substantial bias a "yes" is scored. (N.B. these percentages are arbitrary, not supported by literature).
7	All randomised participants are reported/analysed in the group they were allocated to by randomization for the most important moments of effect measurement (minus missing values) irrespective of noncompliance and co interventions.
8	All the results from all prespecified outcomes have been adequately reported in the published report of the trial. This information is either obtained by comparing the protocol and the report, or in the absence of the protocol, assessing that the published report includes enough information to make this judgment.

9	Groups have to be similar at baseline regarding demographic factors, duration and severity of complaints, percentage of patients with neurological symptoms, and value of main outcome measure(s).
10	If there were no co interventions or they were similar between the index and control groups.
11	The reviewer determines if the compliance with the interventions is acceptable, based on the reported intensity, duration, number and frequency of sessions for both the index intervention and control intervention(s). For example, physiotherapy treatment is usually administered for several sessions; therefore it is necessary to assess how many sessions each patient attended. For single-session interventions (e.g., surgery), this item is irrelevant.
12	Timing of outcome assessment should be identical for all intervention groups and for all primary outcome measures.
13	Other types of biases. For example: -When the outcome measures were not valid. There should be evidence from a previous or present scientific study that the primary outcome can be considered valid in the context of the present. -Industry-sponsored trials. The conflict of interest (COI) statement should explicitly state that the researchers have had full possession of the trial process from planning to reporting without funders with potential COI having any possibility to interfere in the process. If, for example, the statistical analyses have been done by a funder with a potential COI, usually "unsure" is scored.

Footnotes
Higgins 2011

Table 3 Reaching risk of bias judgements in ROBINS-I: pre-intervention and at-intervention domains

Judgement	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions
Low risk of bias (the study is comparable to a well-performed RCT with regard to this domain)	No confounding expected.	All participants who would have been eligible for the target trial were included in the study *and* start of follow-up and start of intervention coincide for all participants.	Intervention status is well-defined and based solely on information collected at the time of intervention.
Moderate risk of bias (the study is sound for an NRCT with regard to this domain but cannot be considered comparable to a well-performed RCT)	Confounding expected, all known important confounding domains appropriately measured and controlled for; *and* reliability and validity of measurement of important domains were sufficient, such that we do not expect serious residual confounding.	Selection into the study may have been related to intervention and outcome, but the authors used appropriate methods to adjust for the selection bias; *or* start of follow-up and start of intervention do not coincide for all participants, but (a) the proportion of participants for which this was the case was too low to induce important bias; (b) the authors used appropriate methods to adjust for the selection bias; or (c) the review authors are confident that the rate (hazard) ratio for the effect of intervention remains constant over time.	Intervention status is well-defined, but some aspects of the assignments of intervention status were determined retrospectively.

Table 3 Reaching risk of bias judgements in ROBINS-I: pre-intervention and at-intervention domains

Judgement	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions
Serious risk of bias (the study has some important problems)	Switches in treatment, co-interventions, or problems with implementation fidelity are apparent and are not adjusted for in the analyses.	Proportions of missing participants differ substantially across interventions; *or* reasons for missing ness differ substantially across interventions; *and* missing data were addressed inappropriately in the analysis; *or* the nature of the missing data means that the risk of bias cannot be removed through appropriate analysis.	The methods of outcome assessment were not comparable across intervention groups; *or* the outcome measure was subjective (i.e. likely to be influenced by knowledge of the intervention received by study participants) and was assessed by outcome assessors aware of the intervention received by study participants; *or* error in measuring the outcome was related to intervention status.
Critical risk of bias (the study is too problematic to provide any useful evidence on the effects of the intervention)	Substantial deviations from the intended intervention are present and are not adjusted for in the analysis.	(Unusual) There were critical differences between interventions in participants with missing data that were not, or could not, be addressed through appropriate analysis.	The methods of outcome assessment were so different that they cannot reasonably be compared across intervention groups.
No information on which to base a judgement about risk of bias for this domain	No information is reported on whether there is deviation from the intended intervention.	No information is reported about missing data or the potential for data to be missing.	No information is reported about the methods of outcome assessment.

Source:
Sterne 2016.

Footnotes
Abbreviations:
NRCT: non-randomised controlled trial
RCT: randomised controlled trial

Table 4 Reaching risk of bias judgements in ROBINS-I: postintervention domains

Judgement	Bias due to deviation from intended intervention	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result
Low risk of bias (the study is comparable to a well-performed RCT with regard to this domain)	No bias due to deviation from the intended intervention is expected, e.g. if both the intervention and comparator are implemented over a short time period, and subsequent interventions are part of routine medical care, or if the specified comparison relates to initiation of intervention regardless of whether it is continued.	Data were reasonably complete;*or* proportions of and reasons for missing participants were similar across intervention groups;*or* analyses that addressed missing data are likely to have removed any risk of bias.	The methods of outcome assessment were comparable across intervention groups;*and* the outcome measure was unlikely to be influenced by knowledge of the intervention received by study participants (i.e. is objective) *or* the outcome assessors were unaware of the intervention received by study participants;*and* any error in measuring the outcome is unrelated to intervention status.	There is clear evidence (usually through examination of a pre-registered protocol or statistical analysis plan) that all reported results correspond to all intended outcomes, analyses, and subcohorts.

Table 4 Reaching risk of bias judgements in ROBINS-I: postintervention domains

Judgement	Bias due to deviation from intended intervention	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result
Moderate risk of bias (the study is sound for an NRCT with regard to this domain but cannot be considered comparable to a well-performed RCT)	Bias due to deviation from the intended intervention is expected, and switches, co-interventions, and some problems with intervention fidelity are appropriately measured and adjusted for in the analyses. Alternatively, most (but not all) deviations from intended intervention reflect the natural course of events after initiation of intervention.	Proportions of missing participants differ across interventions;*or* reasons for missing ness differ minimally across interventions;*and* missing data were not addressed in the analysis.	The methods of outcome assessment were comparable across intervention groups;*and* the outcome measure is only minimally influenced by knowledge of the intervention received by study participants;*and* any error in measuring the outcome is only minimally related to intervention status.	The outcome measurements and analyses are consistent with an a priori plan; or are clearly defined and both internally and externally consistent;*and* there is no indication of selection of the reported analysis from among multiple analyses;*and* there is no indication of selection of the cohort or subgroups for analysis and reporting on the basis of the results.
Serious risk of bias (the study has some important problems)	Switches in treatment, co-interventions, or problems with implementation fidelity are apparent and are not adjusted for in the analyses.	Proportions of missing participants differ substantially across interventions;*or* reasons for missing ness differ substantially across interventions;*and* missing data were addressed inappropriately in the analysis;*or* the nature of the missing data means that the risk of bias cannot be removed through appropriate analysis.	The methods of outcome assessment were not comparable across intervention groups;*or* the outcome measure was subjective (i.e. likely to be influenced by knowledge of the intervention received by study participants) and was assessed by outcome assessors aware of the intervention received by study participants;*or* error in measuring the outcome was related to intervention status.	Outcome measurements or analyses are internally or externally inconsistent;*or* there is a high risk of selective reporting from among multiple analyses;*or* the cohort or subgroup is selected from a larger study for analysis and appears to be reported on the basis of the results.

Table 4 Reaching risk of bias judgements in ROBINS-I: postintervention domains

Judgement	Bias due to deviation from intended intervention	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result
Critical risk of bias (the study is too problematic to provide any useful evidence on the effects of the intervention)	Substantial deviations from the intended intervention are present and are not adjusted for in the analysis.	(Unusual) There were critical differences between interventions in participants with missing data that were not, or could not, be addressed through appropriate analysis.	The methods of outcome assessment were so different that they cannot reasonably be compared across intervention groups.	There is evidence or strong suspicion of selective reporting of results, and the unreported results are likely to be substantially different from the reported results.
No information on which to base a judgement about risk of bias for this domain	No information is reported on whether there is deviation from the intended intervention.	No information is reported about missing data or the potential for data to be missing.	No information is reported about the methods of outcome assessment.	There is too little information to make a judgement (e.g. if only an abstract is available for the study).

*Source:*Sterne 2016.

Table 5 Characteristics of included studies [ordered by study ID] and risk of bias for RCTs

Abrishamkar 2018	
Methods	Study design: randomised controlled trial, parallel design. Setting: hospital, single centre. Country: Iran.
Participants	Randomised/available for analysis: 70 patients/ 57 patients. % Female: 20.7% nucleoplasty group, 14.3% open discectomy group. Age: (years, mean and SD): 44.9 (9.4) nucleoplasty group, 41.3 (7.7) open discectomy group. Duration of disease:(months, mean and SD): 11.4 (7) nucleoplasty group, 12.4 (9.6) open discectomy group. Inclusion criteria: suffering from a single cervical disc herniation, need to surgery to release the pressure on spinal root, existence of a cervical disc herniation needy to surgery, no previous surgery on cervical spine, age <60, and not having spinal canal stenosis. Exclusion criteria: the authors of this study only described the criteria of entering the study.
Interventions	Intervention group: Nucleoplasty, N= 35. Reference group: Open discectomy, N=35. In open discectomy, patients were done in knee chest position and then operation was done under fenestration. In this study, all patients were operated by spinal anesthesia and by one surgeon.
Outcomes	Measured at baseline, 14 days, 1 month, 2 months, 3 months, and 6 months: • Pain • Recovery
Notes	Funding sources: none declared. Conflict of interest: none reported. Full text language: English.
	RISK OF BIAS **Random sequence generation (selection bias)**
Unclear risk of bias	Quote: Then, they were distributed into two groups of nucleoplasty and surgery with the use of allocated random block method. After their admission in surgery room, first group treated by classic method of cervical disc and second group was treated by nucleoplasty method. Comment: the method used for sequence generation unclear.
	Allocation concealment (selection bias)
Unclear risk of bias	Comment: no information available
	Blinding of participants (performance bias)
Unclear risk of bias	Comment: blinding of participants was not possible. Cochrane Handbook: lack of blinding of participants, carers or people delivering the interventions may cause bias if it leads to deviations from intended interventions. No information on deviations from the intended interventions.
	Blinding of health care providers (performance bias)
Unclear risk of bias	Comment: blinding of health care providers was not possible. Cochrane Handbook: lack of blinding of participants, carers or people delivering the interventions may cause bias if it leads to deviations from intended interventions. No information on deviations from the intended interventions.

	Blinding of outcome assessment (detection bias) **All outcomes**
High risk of bias	Comment: all outcomes were patient-reported, and patients were not blinded. Cochrane Handbook: The potential for bias cannot be ignored even if the outcome assessor cannot be blinded. The outcome assessment is potentially influenced by knowledge of intervention received, leading to a judgement of at least 'Some concerns'. Review authors will need to judge whether it is likely that participants' reporting of the outcome was influenced by knowledge of intervention received, in which case risk of bias is considered high. Judgement: concern that lack of blinding would have influenced the outcome.
	Incomplete outcome data (attrition bias) **All outcomes**
Low risk of bias	Quote: 70 persons who suffered from cervical disc were analysed of which 13 patients were omitted from study because of not referring to the hospital (6 patients from nucleoplasty method and 7 patients from classic surgery) Comment: 6/35 (17%) in the nucleoplasty group and 7/35 (20%) in the surgery group were loss to follow up. Reasons not reported ('discontinued intervention').
	Selective reporting (reporting bias)
Unclear risk of bas	Comment: Study protocol was not available, and the study was inadequately reported.
	Other bias
Low risk of bias	Comment: the study appears to be free of other sources of bias.
Birnbaum 2009	
Methods	Design: controlled clinical trial. Setting: orthopaedic clinic. Country: Germany.
Participants	Randomised/available for analysis: not applicable/ 59 patients. % Female: 62% nucleoplasty group, 70% conservative treatment group. Age (years, mean and range): 36 (23-49) nucleoplasty group, 54 (25-56) conservative treatment group. Duration of disease: not reported. Inclusion criteria: MRI proven contained disc herniation, arm pain, and a disc height over 50%. Exclusion criteria: disc height <50%, evidence of severe disc degeneration, spinal fracture or tumour and moderate/severe spinal stenosis.
Interventions	Intervention group: Nucleoplasty, N= 29. Reference group: Conservative treatment with medical and physical therapy, N=30.
Outcomes	Measured at baseline, 1 day, 1 week, 1 month, 3 months, 6 months, 12 months and 24 months: • Pain

Notes	Funding sources: none declared. Conflict of interest: none declared. Full text language: English. **RISK OF BIAS** No risk of bias assessments have been added for this study.
Cesaroni 2010	
Methods	Study design: randomised controlled trial, parallel design. Setting: Clinic for neurosurgery. Country: Italy.
Participants	Randomised/available for analysis: 120 patients/ 115 patients. % Female: woman (%) 62.9% nucleoplasty group, 52.8% conservative treatment group. Age (years, mean and SD): 45.03 (10.72) nucleoplasty group and 47.43 (11.49) conservative treatment group. Duration of disease: not reported Inclusion criteria: MRI proven contained disc herniation, age between 18 and 75 years old, unresolved symptoms after at least 30 days of failed conservative treatment and neck/arm pain VAS score of >50 on a scale of 0–100. Exclusion criteria: Evidence of an extruded or sequestered disc herniation, history of anterior fusion in the cervical level to be treated, spinal fracture, tumour, or infection, a central cord lesion in the cervical spine, progressive neurological deficit, focal protrusion exceeding one-third of the spinal canal, hyperostosis causing concurrent foraminal stenosis at the symptomatic level, myotomal deficit with motor strength less than 4/5, disc height reduction of ≤ 50% (which indicated total degeneration and treatment via fusion), and carotid stenosis or significant plaque-like carotid disease. Additional exclusion criteria included a planned or suspected pregnancy within the study timeframe, a cardiac pacemaker, automatic defibrillator, or any peripheral stimulator leads within the neck area, a known allergy to contrast media or drugs to be used in the procedure, psychological instability or undergoing anti-psychotic therapy, or involvement in litigation related to arm and neck pain.
Interventions	Intervention group: Nucleoplasty, N= 62. Reference group: Conservative Treatment: This group received an array of conservative treatment therapies, depending on the patient's condition and preference. These included transcutaneous electrical nerve stimulation, progressive neck mobilisation (both active and passive) accompanied by a gradual reduction in collar usage, postural rehabilitation of the Mezieres technique, as well as analgesics and/or NSAIDs, N= 58.
Outcomes	Measured at baseline, 6 weeks, 3 months, 6months and 12 months: • Pain • Neck-related functional status • Global health status • Adverse effects
Notes	Funding sources: Financial grant from ArthroCare Corporation that covering the costs of clerical staff to collect data. Conflict of interest: None reported. Full text language: English.

	RISK OF BIAS **Random sequence generation (selection bias)**
Unclear risk of bias	Quote: Subjects were randomly assigned to receive either nucleoplasty or conservative care (CC). In order to randomize, sealed envelopes were labelled with consecutive numbers and remained sealed until a given subject was to be assigned treatment. Immediately upon study enrolment, subjects were assigned treatment by opening the envelopes in sequential order. Comment: envelopes were labelled with consecutive numbers, but unclear how the sequence of the allocation was generated. Likely to be predictable, but unclear.
	Allocation concealment (selection bias)
Unclear risk of bias	Quote: Subjects were randomly assigned to receive either nucleoplasty or conservative care (CC). In order to randomize, sealed envelopes were labelled with consecutive numbers and remained sealed until a given subject was to be assigned treatment. Immediately upon study enrolment, subjects were assigned treatment by opening the envelopes in sequential order. Comment: unclear what the meaning of the consecutive numbering is, and opening the envelopes in sequentially order. Likely to be predictable, but unclear.
	Blinding of participants (performance bias)
Unclear risk of bias	Comment: blinding of participants was not possible. Cochrane Handbook: lack of blinding of participants, carers or people delivering the interventions may cause bias if it leads to deviations from intended interventions. No information on deviations from the intended interventions.
	Blinding of health care providers (performance bias)
Unclear risk of bias	Comment: blinding of health care providers was not possible. Cochrane Handbook: lack of blinding of participants, carers or people delivering the interventions may cause bias if it leads to deviations from intended interventions. No information on deviations from the intended interventions.
	Blinding of outcome assessment (detection bias) **All outcomes**
High risk of bias	Comment: all outcomes were patient-reported, and patients were not blinded. Cochrane Handbook: The potential for bias cannot be ignored even if the outcome assessor cannot be blinded. The outcome assessment is potentially influenced by knowledge of intervention received, leading to a judgement of at least 'Some concerns'. Review authors will need to judge whether it is likely that participants' reporting of the outcome was influenced by knowledge of intervention received, in which case risk of bias is considered high. Judgement: concern that lack of blinding would have influenced the outcome.
	Incomplete outcome data (attrition bias) **All outcomes**
Low risk of bias	Comment: 5/58 subjects in the conservative care group did not undergo treatment after random assignment, but were included in the analysis. For time points 6M and 12M one patient in each group was loss to follow up/not included in the analysis (Table 2). Missing data was addressed in these Generelized Etimating Equations models by using maximum likelihood estimation for longitudinal models under "missing at random" assumptions.

	Selective reporting (reporting bias)
Unclear risk of bas	Comment: no registered or published protocol available. Pre-defined outcomes are reported in the paper.
	Other bias
Low risk of bias	Comment: the study appears to be free of other sources of bias.
De Rooij 2020	
Methods	Design: randomised controlled trial, parallel design. Setting: hospital. Country: Netherlands.
Participants	Randomised/available for analysis: 48 patients/48 patients. % Female: 58.3% nucleoplasty group, 54.2% anterior cervical discectomy group. Age (years, mean): 47 (9.24) nucleoplasty group, 50 (9.24) anterior cervical discectomy group. Duration of disease (months, mean): 18.17 (23.9) nucleoplasty group, 22.8 (30.9) anterior cervical discectomy group. Inclusion criteria: radicular pain of the lower cervical spine (C4 – C7) as a result of a single-level contained soft-disc hernia with or without neck pain and without improvement after at least 8 weeks of CT. In addition, the intensity of their radicular arm pain had to be at least 50 millimetres (mm) on a visual analog scale (VAS) (0 = no pain and 100 = the worst pain imaginable) Exclusion criteria: previous spinal surgery in the cervical region, an extruded disc fragment, a bony spur, a calcified disc, or severe degenerative disc disease with more than 50 percent loss of disc height.
Interventions	Intervention group: Nucleoplasty, N=24. Reference group : Anterior cervical discectomy, N=24.
Outcomes	Measured at baseline, 1 week, 3 months and 12 months: • Arm pain • Neck pain • Neck-related functional status • Global health status - physical function • Global health status - social function • Recovery • Adverse effects
Notes	Funding sources: none declared. Conflict of interest: none declared. Full text language: English.
	RISK OF BIAS **Random sequence generation (selection bias)**
Low risk of bias	Quote: The patients were randomized according to a computer-generated non-stratified block randomization program (www. randomization.com).
	Allocation concealment (selection bias)
Low risk of bias	Quote: An independent observer, who was not involved in the patients' outcome assessments, provided the trial coordinator with sealed envelopes containing the randomization assignments.

	Blinding of participants (performance bias)
Unclear risk of bias	Quote: Due to the nature of the interventions, it was not possible to blind the interventionists and the patients. The data were analysed blindly. Comment: Cochrane Handbook: lack of blinding of participants, carers or people delivering the interventions may cause bias if it leads to deviations from intended interventions. No information on deviations from the intended interventions.
	Blinding of health care providers (performance bias)
Unclear risk of bias	Quote: Due to the nature of the interventions, it was not possible to blind the interventionists and the patients. The data were analysed blindly. Comment: Cochrane Handbook: lack of blinding of participants, carers or people delivering the interventions may cause bias if it leads to deviations from intended interventions. No information on deviations from the intended interventions.
	Blinding of outcome assessment (detection bias) **All outcomes**
High risk of bias	Quote: Due to the nature of the interventions, it was not possible to blind the interventionists and the patients. The data were analysed blindly. Comment: all outcomes were patient-reported. Cochrane Handbook: The potential for bias cannot be ignored even if the outcome assessor cannot be blinded. The outcome assessment is potentially influenced by knowledge of intervention received, leading to a judgement of at least 'Some concerns'. Review authors will need to judge whether it is likely that participants' reporting of the outcome was influenced by knowledge of intervention received, in which case risk of bias is considered high. Judgement: concern that lack of blinding would have influenced the outcome.
	Incomplete outcome data (attrition bias) **All outcomes**
Low risk of bias	Quote: An intention-to-treat (ITT) analysis with last observation carried forward and a per protocol (PP) analysis were performed, in which we compared the outcomes on T2 with those on T0 and T3 to T0. Loss-to-follow up 2/24 in both groups for similar reasons at 3 months (T2), 3/22 in nucleopasty group and 2/22 in anterior cervical discectomy group at 12 months (T3). Comment: some concern as missing data have been imputed by potentially inappropriate measures, but not enough to judge high risk of bias. Lack of engagement with study (reason for dropout for most patients who were loss to follow up) not likely associated with true value, i.e. pain level is not likely related to drop out.
	Selective reporting (reporting bias)
Low risk of bas	Comment: No deviations from protocol.
	Other bias
Low risk of bias	Comment: the study appears to be free of other sources of bias.
Halim 2016	
Methods	Design: randomised controlled trial, parallel design. Setting: hospital. Country: Netherlands.

Participants	Randomised/available for analysis: 38 patients/ 34 patients. % Female: 35% nucleoplasty group, 37.5% pulsed radio frequency group. Age (years, mean): 52.4 nucleoplasty group, 49.5 pulsed radio frequency group. Duration of disease (months, mean): 11.9 nucleoplasty group, 12.1 pulsed radio frequency group. Inclusion criteria: contained, single-level cervical disk herniation diagnosed on recent MRI (< 4 weeks), who failed conservative treatment and reported radicular pain (≥ 50 mm on 100 mm Visual Analogue Scale for pain [VAS-100 mm]) with or without neck pain corresponding to the herniated level, and a disk height over 50% of adjacent level. Inclusion criteria: Patients who are diagnosed with a contained-single-level cervical disk herniation on recent MRI (<4 weeks), who failed conservative treatment and reported radicular pain ≥50 mm on 100 mm VAS) with or without neck pain corresponding to the herniated level, and a disk height over 50% of adjacent level. Exclusion criteria: No electromyographic examination was performed, but participants who did not respond (> 50% temporary pain relief for at least 30 minutes) to a diagnostic nerve block15 placed with local anaesthetic (Lidocaine 1% 1 mL) at the level identified with history taking and MRI were excluded. Patients with extruded disk fragmentation, cervical spondylolisthesis, or spinal canal stenosis and patients with previous surgery at the index cervical disk herniation level were also excluded.
Interventions	Intervention group: Nucleoplasty, N=17. Reference group: Pulsed radio frequency (PRF) treatment of the dorsal root ganglion, N=17. PRF is a percutaneous procedure of the dorsal root ganglion to treat cervical radicular pain in which the nerve is exposed to a high-frequency electric field with a maximal temperature of the electrode tip of 43◦C . Rehabilitation procedures were equal to both treatment groups.
Outcomes	Measured at 1 month, 2 months and 3 months: • Pain • Neck-related functional status • Recovery measured by global perceived effect • Adverse effects
Notes	Funding sources: Financial grant from ArthroCare Corporation that covering the costs of clerical staff to collect data. Conflict of interest: None reported. Full text language: English.
	RISK OF BIAS **Random sequence generation (selection bias)**
Low risk of bias	Comment: the study authors did not describe the method of randomisation in their article and protocol (ClinicalTrials.gov Identifier:NCT01797172). However, the corresponding author of this study gave us additional information about the randomization process.

	Allocation concealment (selection bias)
Low risk of bias	Comment: the study authors did not describe the method of allocation concealment in their article and protocol (ClinicalTrials.gov Identifier: NCT01797172). But the corresponding author of this study gave us additional information that both the randomization list and sealed and labelled envelopes were supervised by an independent assistant at the pain management outpatient clinic. This independent assistant coordinated the randomization and planning of the treatment. At the point of randomization, the lowest available study number will be assigned to the patient and correctly entered into the Case Report Forms (CRFs). The assistant will open the appropriate envelope according to the assigned patient study number.
	Blinding of participants (performance bias)
Low risk of bias	Comment: the study authors did not mention blinding of participants in their article, though they mentioned it in their protocol (ClinicalTrials.gov Identifier:NCT01797172: masking of participants and outcome assessors). The corresponding author of this study gave us additional information and responded that the involved researcher (outcome assessor) was only being informed via the CRF whether the patient was assigned to group one or two, without knowing which group contains what type of treatment. By following this procedure as well participants as the outcome assessor were blinded for the allocated treatment. This provides the possibility for blinded completion of the questionnaires during follow-up visits and blinded data-analysis.
	Blinding of health care providers (performance bias)
Unclear risk of bias	Comment: it was not possible to blind the interventionists. Cochrane Handbook: lack of blinding of participants, carers or people delivering the interventions may cause bias if it leads to deviations from intended interventions. No information on deviations from the intented interventions.
	Blinding of outcome assessment (detection bias) **All outcomes**
Low risk of bias	Comment: patients and outcome assessor were blinded, see comment Blinding of participants (performance bias).
	Incomplete outcome data (attrition bias) **All outcomes**
High risk of bias	Comment: 3/20 (15%) participants were lost to follow up in the intervention group and 7/24 (29%) participants in the control group. Reasons for drop out not provided. Possible selective drop out. "Outliers were filtered out by checking if all data were in the range of mean 2 SD." Unclear what is meant by this statement.
	Selective reporting (reporting bias)
Low risk of bas	Comment: the protocol number from clinical trials.gov was not mentioned in their article, but the corresponding author gave us the link of their registered protocol (https://clinicaltrials.gov/ct2/show/NCT01797172). We compared the pre-specified outcomes with the reported outcomes and concluded that they did not report other outcome measures.

	Other bias
Low risk of bias	Comment: the study appears to be free of other sources of bias.
Nardi 2005	
Methods	Design: controlled clinical trial. Setting: outpatient clinic. Country: Italy .
Participants	Randomised/available for analysis: Not applicable/ at baseline there were 50 patients in the nucleoplasty group and 20 patients in the conservative group. Gender: not reported. Age: not reported. Duration of disease: not reported. Inclusion criteria: disc protrusion or contained herniated disc not larger than 3 mm and not compromising more than 1/5 of the central spinal canal demonstrated on a magnetic resonance imaging (MRI). All patients reported to have persistent cervical or unilateral arm pain for a minimum of three months and had failed previous conservative treatment. Exclusion criteria: patients affected by spinal fractures, acquired stenosis, tumour, advanced spondylosis resulting in osseous foraminal stenosis or disc space collapse or with previous spinal surgery on the same level.
Interventions	Intervention group: Nucleoplasty, N= 50. Reference group: Medical therapy consisted of anti-inflammatory drugs and corti sonics for a period between 20 to 45 days, physical therapy included wearing of a Schanz collar for at least 30 days, N=20.
Outcomes	Measured at baseline, day 1, 1 week and 60 days after intervention: • Pain • The study authors presented their VAS results via percentages of recovery.
Notes	Funding sources: none declared. Conflict of interest: none reported. Full text language: English.
	RISK OF BIAS No risk of bias assessments have been added for this study.

Footnotes
Note: In the ‹Characteristics of studies› tables, all outcomes mentioned by the study authors are given.
Abbreviations:
MRI: Magnetic Resonance Imaging
NSAIDs: Non-Steroidal Anti-Inflammatory Drugs
SD: Standard Deviation

Table 6 Risk of bias tables for NRCTs (judged with ROBINS-I)

Birnbaum 2009		
Bias	**Authors' judgement**	**Support for judgement**
Bias due to confounding	CRITICAL RISK	No control of confounding variables
Bias in selection of participants into the study	SERIOUS RISK	Possible influence of intervention and outcome on selection into the study
Bias in classification of interventions	SERIOUS RISK	Some concerns about intervention status definition
Bias due to deviations from intended intervention	LOW RISK	Unlikely deviation from the interventions
Bias due to missing data	LOW RISK	Outcome data available for nearly all patients Quote: three participants in the surgical group get out of sight after 24 months. Totally 26 patients in the nucleoplasty group could be follow-up after 24 months. Comment: the percentage of withdrawals and drop-outs did not exceed 20% for short-term follow-up and 30% for long-term follow-up.
Bias in measurement of outcomes	SERIOUS RISK	Potential subjectivity of outcome measures, determined by treating clinicians
Bias in selection of the reported result	MODERATE RISK	No evidence of selected reporting, but no detailed protocol
OVERAL RISK OF BIAS	CRITICAL RISK study	
Nardi 2005		
Bias	**Authors' judgement**	**Support for judgement**
Bias due to confounding	CRITICAL RISK	No control of confounding variables
Bias in selection of participants into the study	SERIOUS RISK	Influence of intervention and outcome on selection into the study
Bias in classification of interventions	SERIOUS RISK	Some concerns about intervention status definition
Bias due to deviations from intended intervention	LOW RISK	Unlikely deviation from the interventions

Table 6 Risk of bias tables for NRCTs (judged with ROBINS-I)

Bias	Authors' judgement	Support for judgement
Bias due to missing data	LOW RISK	Outcome data available for nearly all patients Quote: 1 participant was lost at last follow up in the control group Comment:the percentage of withdrawals and drop-outs did not exceed 20% for short-term follow-up
Bias in measurement of outcomes	NO INFORMATION	Unclear information on outcome assessment, only tools and timing are mentioned, not who performs the assessments
Bias in selection of the reported result	MODERATE RISK	No evidence of selected reporting, but no detailed protocol
OVERAL RISK OF BIAS	CRITICAL RISK study	

Table 7 Characteristics of excluded studies

Azzazi 2010	
Reason for exclusion	No RCT or NRCT
Bonaldi 2006	
Reason for exclusion	No RCT or NRCT
Cesaroni 2011	
Reason for exclusion	No RCT or NRCT
Ierardi 2020	
Reason for exclusion	No RCT or NRCT
Li 2008	
Reason for exclusion	No RCT or NRCT
Sim 2011	
Reason for exclusion	No RCT or NRCT
Slipman 2003	
Reason for exclusion	No RCT or NRCT
Yan 2010	
Reason for exclusion	No RCT or NRCT

FIGURES

Figure 1: Study flow diagram

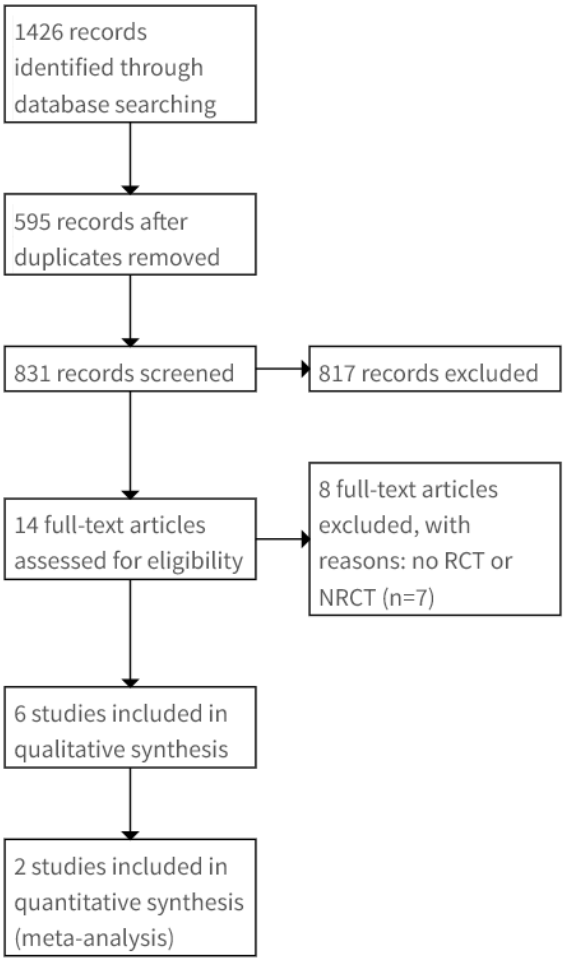


Figure 2: Risk of bias summary RCTs

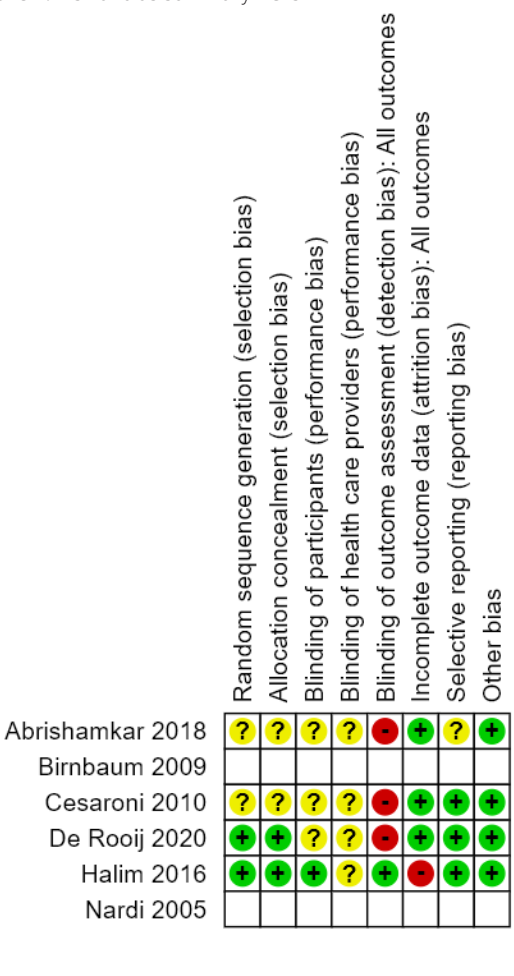
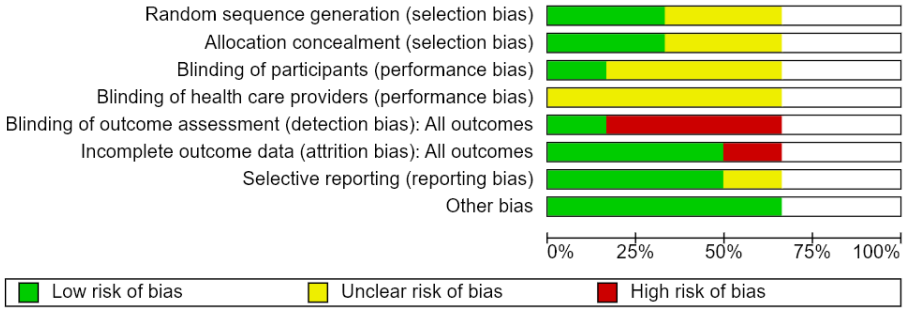


Figure 3: Risk of bias graph RCT



Risk of bias summary: review authors' judgements about each risk of bias item for each included RCT.

Figure 4: Risk of bias summary NRCTs

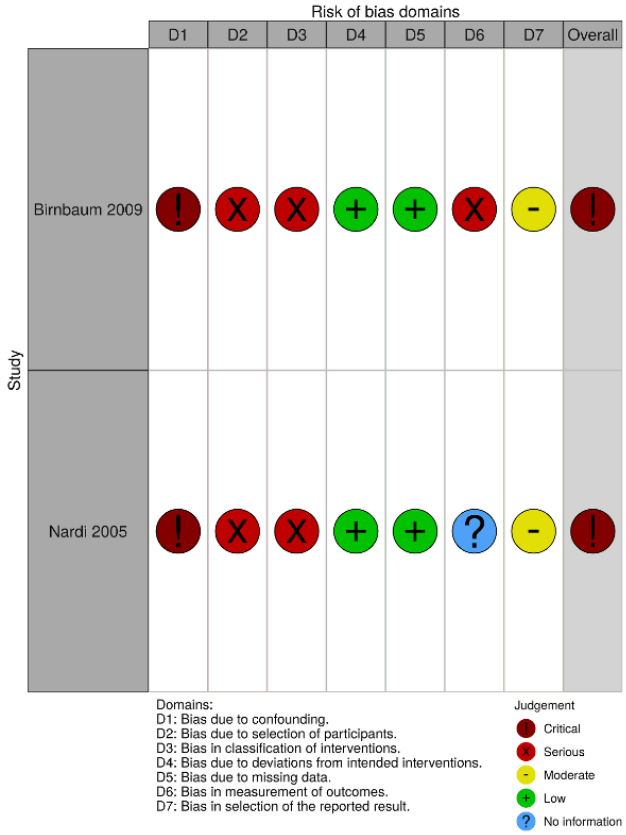
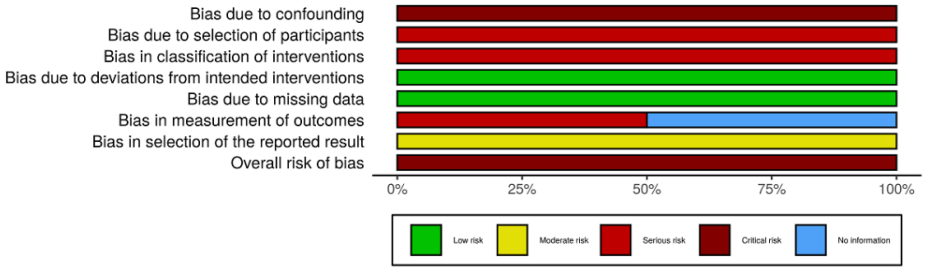


Figure 5: Risk of bias graph NRCT

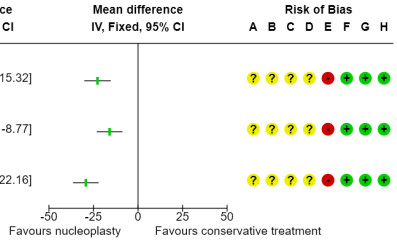


ANALYSIS COMPARISONS

1 Nucleoplasty compared to conservative treatment for patients with cervical radiculair pain due to a disc herniation

Analysis 1.1: Pain intensity (VAS pain score)

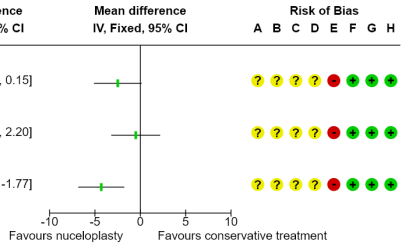
Study or Subgroup	Cervical nucleoplasty Mean	SD	Total	Conservative treatment Mean	SD	Total	Mean difference IV, Fixed, 95% CI
1.1.1 ≤ 3 months							
Cesaroni 2010	-53.16	21.57	62	-30.45	19.72	58	-22.71 [-30.10 , -15.32]
1.1.2 ≥3 months and ≤ 12 months							
Cesaroni 2010	-56.22	20.54	61	-40.26	19.32	57	-15.96 [-23.15 , -8.77]
1.1.3 ≥ 12 months							
Cesaroni 2010	-65.73	17.49	61	-36.45	21.59	57	-29.28 [-36.40 , -22.16]



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants (performance bias)
(D) Blinding of health care providers (performance bias)
(E) Blinding of outcome assessment (detection bias)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Analysis 1.2: Neck-related functional status (NDI)

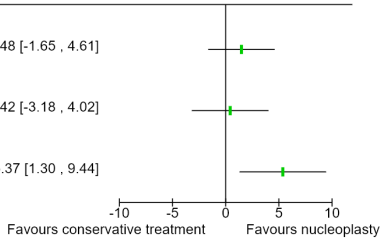
Study or Subgroup	Nucleoplasty Mean	SD	Total	Conservative treatment Mean	SD	Total	Mean difference IV, Fixed, 95% CI
1.2.1 ≤ 3 months							
Cesaroni 2010	-11.75	8.5	62	-9.27	6.09	58	-2.48 [-5.11 , 0.15]
1.2.2 ≥ 3 months and ≤ 12 months							
Cesaroni 2010	-13.36	8.75	61	-12.86	6.04	57	-0.50 [-3.20 , 2.20]
1.2.3 ≥ 12 months							
Cesaroni 2010	-16.7	2.26	61	-12.4	9.51	57	-4.30 [-6.83 , -1.77]



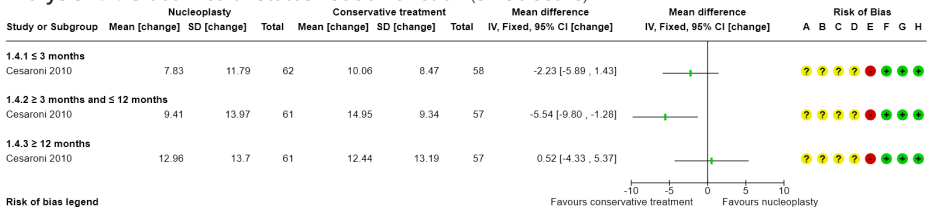
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants (performance bias)
(D) Blinding of health care providers (performance bias)
(E) Blinding of outcome assessment (detection bias)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Analysis 1.3: Global health status - physical function (SF-36 score)

Study or Subgroup	Nucleoplasty Mean	SD	Total	Conservative treatment Mean	SD	Total	Mean difference IV, Fixed, 95% CI
1.3.1 ≤ 3 months							
Cesaroni 2010	10.08	10.12	62	8.6	7.19	58	1.48 [-1.65 , 4.61]
1.3.2 ≥ 3 months and ≤ 12 months							
Cesaroni 2010	12.25	11.77	61	11.83	7.96	57	0.42 [-3.18 , 4.02]
1.3.3 ≥ 12 months							
Cesaroni 2010	15.15	11.42	61	9.78	11.12	57	5.37 [1.30 , 9.44]

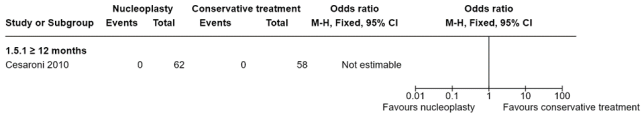


Analysis 1.4: Global health status - social function (SF-36 score)



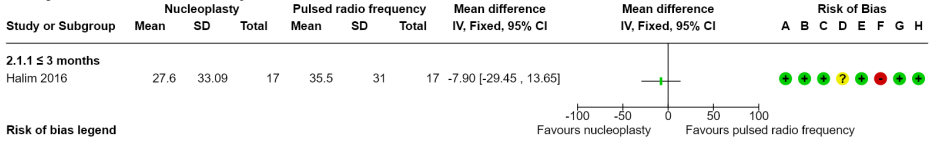
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants (performance bias)
(D) Blinding of health care providers (performance bias)
(E) Blinding of outcome assessment (detection bias)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Analysis 1.5: Adverse effects



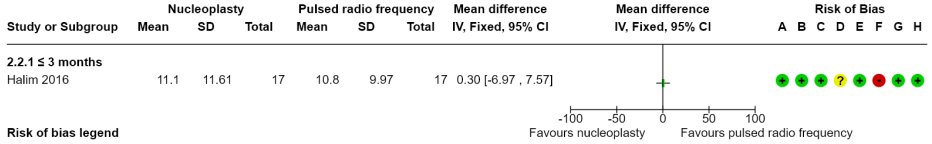
2 Nucleoplasty compared to pulsed radio frequency of the dorsal root ganglion for patients with cevical radiculair pain due to disk herniation

Analysis 2.1: Pain intensity



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants (performance bias)
(D) Blinding of health care providers (performance bias)
(E) Blinding of outcome assessment (detection bias)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Analysis 2.2: Neck-related functional status (NDI)



Risk of bias legend
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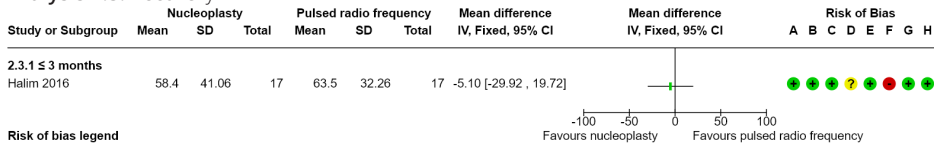
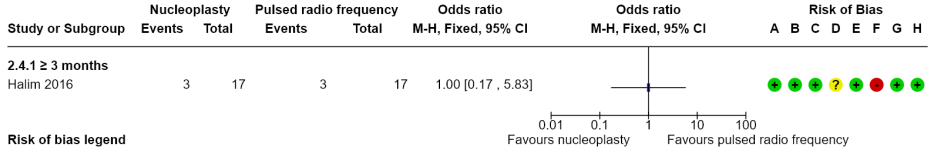
(D) Blinding of health care providers (performance bias)
(E) Blinding of outcome assessment (detection bias)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Analysis 2.3: Recovery



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants (performance bias)
(D) Blinding of health care providers (performance bias)
(E) Blinding of outcome assessment (detection bias)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Analysis 2.4: Adverse effects



Risk of bias legend
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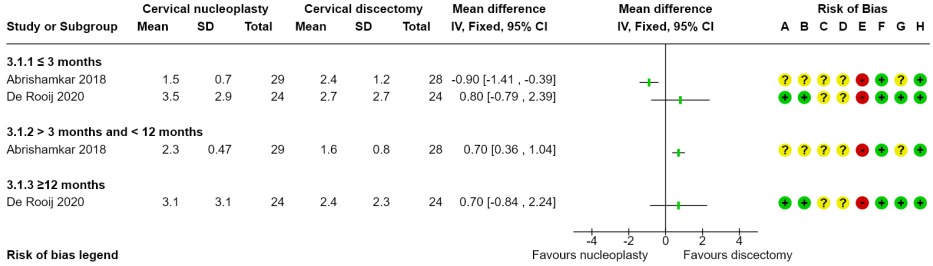
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

3 Nucleoplasty compared to discectomy for patients with cervical radiculair pain due to a disc herniation

Analysis 3.1: Arm pain intensity



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
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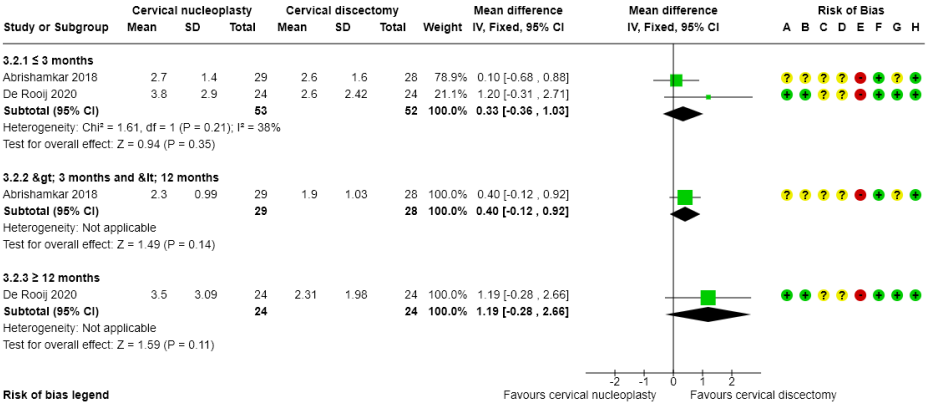
(D) Blinding of health care providers (performance bias)
(E) Blinding of outcome assessment (detection bias)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Analysis 3.2: Neck pain intensity



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
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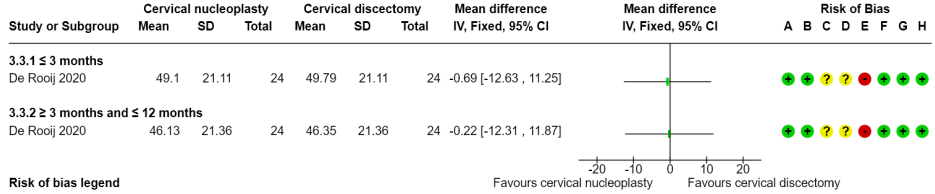
(D) Blinding of health care providers (performance bias)
(E) Blinding of outcome assessment (detection bias)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Analysis 3.3: Neck-related functional status (NDI)



Risk of bias legend
(A) Random sequence generation (selection bias)
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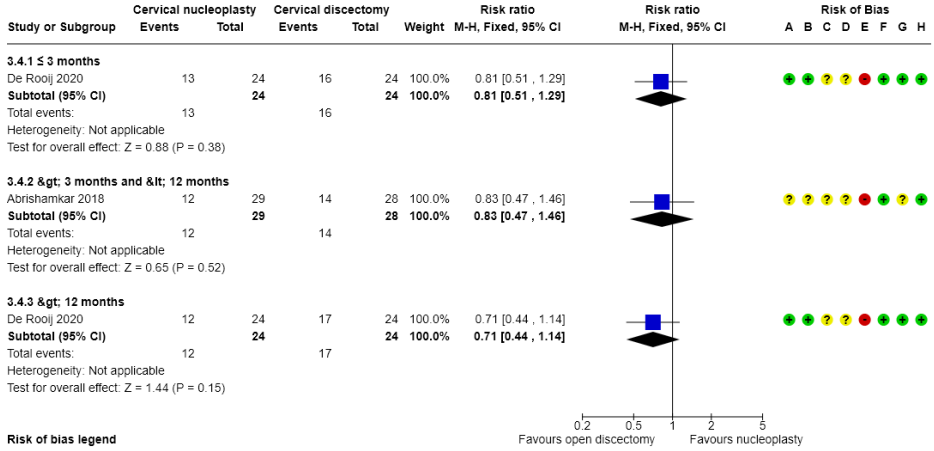
(E) Blinding of outcome assessment (detection bias)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Analysis 3.4: Recovery



Risk of bias legend
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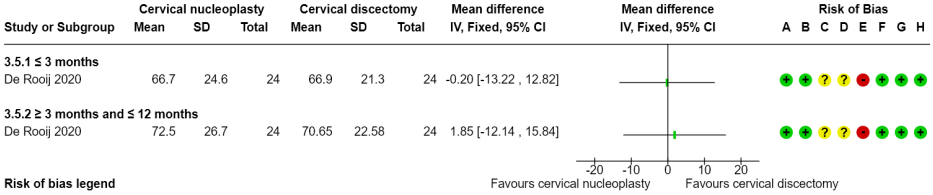
(B) Allocation concealment (selection bias)
(C) Blinding of participants (performance bias)
(D) Blinding of health care providers (performance bias)
(E) Blinding of outcome assessment (detection bias)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Analysis 3.5: Global health status - physical function (SF-36 score)



Risk of bias legend
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(B) Allocation concealment (selection bias)
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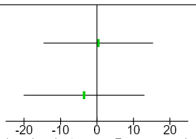
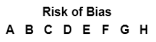
(D) Blinding of health care providers (performance bias)
(E) Blinding of outcome assessment (detection bias)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Analysis 3.6: Global health status - social function (SF-36 score)

Study or Subgroup	Cervical nucleoplasty Mean	SD	Total	Cervical discectomy Mean	SD	Total	Mean difference IV, Fixed, 95% CI
3.6.1 ≤ 3 months							
De Rooij 2020	66.67	25.71	24	66.3	27.29	24	0.37 [-14.63 , 15.37]
3.6.2 ≥ 3 months and ≤ 12 months							
De Rooij 2020	68.75	29.49	24	72.28	28.93	24	-3.53 [-20.06 , 13.00]

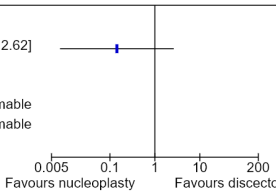




Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants (performance bias)
(D) Blinding of health care providers (performance bias)
(E) Blinding of outcome assessment (detection bias)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Analysis 3.7: Adverse effects

Study or Subgroup	Nucleoplasty Events	Total	Discectomy Events	Total	Risk ratio M-H, Fixed, 95% CI
3.7.1 ≤ 3 months					
De Rooij 2020	0	24	3	24	0.14 [0.01 , 2.62]
3.7.2 ≥ 3 months and ≤ 12 months					
Abrishamkar 2018	0	29	0	28	Not estimable
De Rooij 2020	0	24	0	24	Not estimable



Risk of bias legend
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(B) Allocation concealment (selection bias)
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(D) Blinding of health care providers (performance bias)
(E) Blinding of outcome assessment (detection bias)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Part two

Intervention techniques and preferences

Chapter four

NUCLEOPLASTY FOR THE TREATMENT OF A CONTAINED CERVICAL DISC HERNIATION

J.D. de Rooij
P.S. Gadjradj
J.S. Soria van Hoeve
F.J.P.M. Huygen
H.A. Aukes
B.S. Harhangi

Clin Spine Surg. 2017 Nov; 30(9): 389–391.

Abstract

Cervical radiculopathy is characterized by compression of the roots of the nerve. When conservative treatment fails and symptoms persist or increase in severity, surgical treatment is considered. Anterior cervical discectomy with or without fusion is regarded as the standard treatment for cervical disc herniation. Recently, there is an evolving trend in spinal surgery towards less invasive techniques. Nucleoplasty is a minimally invasive technique in which radiofrequency technology is used for percutaneous decompression. During the last years nucleoplasty has been proven to be a safe and effective treatment to alleviate radiculopathy, caused by a contained disc herniation. Nucleoplasty is usually performed on an outpatient basis and is associated with a fast recovery time. This paper will describe the preoperative and postoperative management of cervical nucleoplasty as well as the surgical technique, accompanied by a video, see references.

Indications

Strict selection criteria of patients are essential for successful treatment. The ideal selection criteria are patients with a symptomatic single-level contained cervical disc herniation's (CDH) and minimally degenerated discs. Contraindications are sequestered disc fragments, stenosis of the neural foramen or spinal canal, primary or metastatic malignancy, discitis, calcified discs, osteophytes, severe degenerative disc disease with >50% loss of disc height, previous operations of the intervertebral disc at the same level, anticoagulant therapy, impaired coagulation and pregnancy. Preoperative screening starts with an x-ray of the cervical spine to exclude osteophytes, possible misalignment of the vertebrae, facet arthropathy, stenosis of the canal, and fracture. Magnetic Resonance imaging (MRI) with T1-and T2-weighting sequences is performed before the PCN procedure to confirm the level of the CDH (See Figure 1).

Operating room set-up

Instruments/Materials Required

- X-ray permeable table.
- Intraoperative fluoroscopy (C-arm).
- ArthroCare introducer cannula, 19 G.
- ArthroCare Coblator IQ SpineWand, surgical device with integrated cable.
- ArthroCare Coablator IQ controller with foot control.

Preoperative Preparation

- One hour before the PCN antibiotic therapy is administered with Cefazoline.
- The patient is placed in a supine position on an x-ray permeable table with head slightly hyper extended.

- The neck is sterilized with a Chloorhexidine 0.5% in alcohol 70% solution.
- The draping starts along the patient's neck using a 40×40 cm^2 Steri-Drape with a 10×12.5 cm^2 adhesive aperture and then drapes are placed to create aseptic conditions.
- The patient is treated under local anesthesia and the procedure is performed under a light intravenous sedation with low dose Remifentanil intravenously.
- A facial mask (oxygen 40%, air 60%) is used. This mask also creates a better breathing space for the patients' comfort during the procedure.
- The patient is monitored during the procedure. Electrocardiogram , blood pressure and oxygen saturation are measured.
- The intraoperative fluoroscopy (C-arm) is positioned on the opposite of the surgeon to obtain anteroposterior (AP), lateral and oblique view

Surgical procedure

Please see the Supplemental Digital Content for the accompanying video of the procedure in the references.

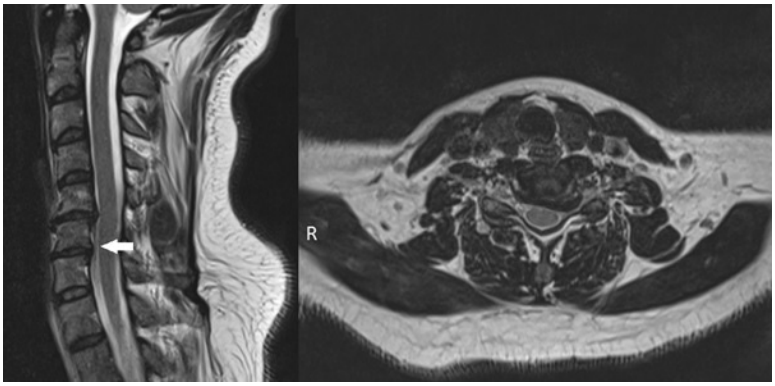

Figure 1: Sagital and axial magnetic resonance imaging of the bulging disc at level C6–C7 left.

Step 1: Marking

The intervertebral space of the CDH is detected with a trocar/needle under fluoroscopic view. The procedure is always performed from the right side to prevent puncture of the esophagus. The surgeon keeps the sternocleidomastoid muscle laterally and the trachea medially and the position of the carotid artery is localized. The introducer cannula (19-G, 7.6 cm) is then inserted under a 45-degree angle medially to the sternocleidomastoid muscle and vessels through an anterior lateral approach, and stopped when the annulus/ nucleus junction is reached. The tip of the cannula stylet is aimed for the center of the nucleus in both the coronal and sagittal planes. AP and lateral x-ray monitoring views confirm the precise positioning of the cannula within the nucleus.

Step 2

Insert the Spine Wand. The stylet is withdrawn from the introducer cannula and replaced with the Spine Wand Co-ablation needle (see Fig. 2). This device is advanced until its tip extends approximately 5 mm beyond the tip of the cannula, in order to ensure that the active portion of the wand is deployed in the center or posterior third of the nucleus pulposus.

Step 3: Ablation

A short initial motoric stimulation (0.5 s) is performed upon wand insertion in the most distal position to ensure correct placement; if stimulation or movement is detected, the device will be repositioned. As the device is drawn back out through the disc, 3 ablation cycles of 10 seconds each will be performed, rotating the device tip 360 degrees each time to form 3 consecutive pockets within the disc. The first coablation cycle is performed most posterior in the disc and confirmed by fluoroscopy, the second coablation cycle is performed 3–5 mm more proximal and the third another 3–5 mm more proximal. These 3 ablation cycles lead to a volumetric reduction of the tissue of the nucleus pulposus, resulting in decompression of the herniated disc. The coablation procedure should be painless; if any pain is experienced during coablation the position ofthe needle is reassessed by fluoroscopy. If the pain persists despite optimal position of the needle the procedure is cancelled.

Step 4: Closure

The 1-mm skin incision is closed with a plaster.

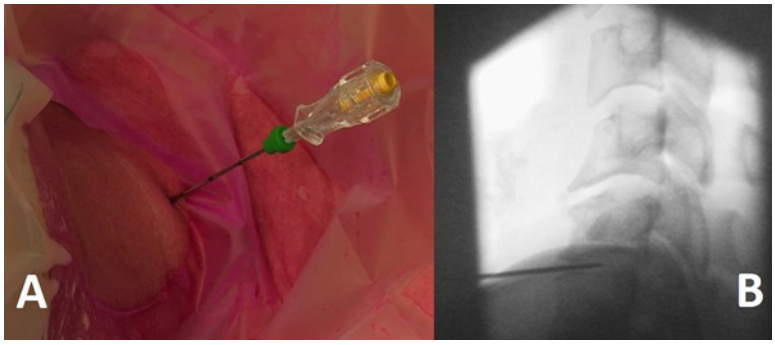

Figure 2: A, The position of the needle. B, The fluoroscopy.

Postoperative protocol

Postoperatively, antibiotic prophylaxis with a cephalosporin is administered to all the patients. To prevent neck edema, patients are treated with a coldpack during 1 hour. Postoperatively, patients are observed during 3 hours bed rest. If necessary, conservative therapies (physical therapy, nonsteroidal anti-inflammatory drugs and analgesics according to the World Health Organisation pain ladder) are prescribed. In

our practice, no collars are applied postoperatively. In the absence of complications, patients are discharged on the same day of the procedure. Heavy lifting, forward bending, twisting of the neck, and severe physical activities are not permitted during the first 2 weeks after the procedure. After 2 weeks the patient is allowed to return to sedentary or light work. In our practice, a follow-up phone call is performed by a nurse, trained in Pain Medicine, 48 hours after the procedure. During this consult pain measured by VAS-scores of the affected arm, neck, shoulder and hand, complications (hoarseness and dysphagia), and use pain medication are evaluated. If necessary, pain medication is adjusted. After 6–8 weeks the patient has a control appointment at our clinic to evaluate the final results.

Complications

As PCN is performed through needle coablation and no structures are ligated, complications rarely occur and data on these complications are scarce. A recent meta-analysis pooled results of 6 studies compromising 638 patients.[1] Among these patients the complication rate was 0.8% which included one complication because of instrument failure. Spondylodiscitis is another reported complication,[2] which can be dealt with antimicrobial therapy. One case of inferior thyroid artery injury is reported.[3]

Pearls and pitfalls

- PCN, compared with surgical treatment, is a less invasive technique which is performed under local anesthetics on an outpatient basis. The procedure is proved to be a safe technique when performed in an experienced center with a dedicated team.
- Before placement of the needle the position of the carotid artery and trachea should be marked to avoid complications. For this reason, the procedure is always performed from the right side to avoid perforation of the esophagus.
- Localizing the exact level by fluoroscopy and placement of the needle in tunnel vision is one of the keys of a successful procedure.
- During treatment of the CDH in the lower cervical region, fluoroscopic visualization can be impaired by over projection of the shoulders. Some traction at the arms can resolve this problem.
- Selecting the correct CDHs for PCN is key for a successful outcome.

References

1. Eichen PM, Achilles N, Konig V, et al. Nucleoplasty, a minimally invasive procedure for disc decompression: a systematic review and meta-analysis of published clinical studies. Pain Physician. 2014;17:E149–E173.
2. Wullems JA, Halim W, van der Weegen W. Current evidence of percutaneous nucleoplasty for the cervical herniated disk: a systematic review. Pain Pract. 2014;14:559–569.
3. Kim JY, Kim IS, Hong JT, et al. Inferior thyroid arterial injury after percutaneous cervical nucleoplasty. Spine J. 2015;15:1495–1496

QR-code Surgical procedure:

Chapter five

ANTERIOR CERVICAL DISCECTOMY WITHOUT FUSION FOR A SYMPTOMATIC CERVICAL DISC HERNIATION

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Abstract

Background

Cervical radiculopathy is characterized by dysfunction of the nerve root usually caused by a cervical disc herniation. The most important symptom is pain, radiating from the neck to the arm. When conservative treatment fails, surgical treatment is indicated to relieve symptoms. During the last decades, multiple fusion techniques have been developed, although without clinical evidence for added value of fusion over non-fusion.

Methods

The surgical procedure of anterior cervical discectomy without fusion is performed step by step, leading to removal of the entire intervertebral disc.

Conclusion

Anterior cervical discectomy without fusion is a safe and effective treatment for cervical disc herniation.

Relevant surgical anatomy

There are several structures which the neurosurgeon must be aware of when performing an anterior cervical discectomy. These include the sternocleidomastoid muscle (SCM), the carotid artery, the internal jugular vein, the esophagus and the vagus nerve (See figure 1).

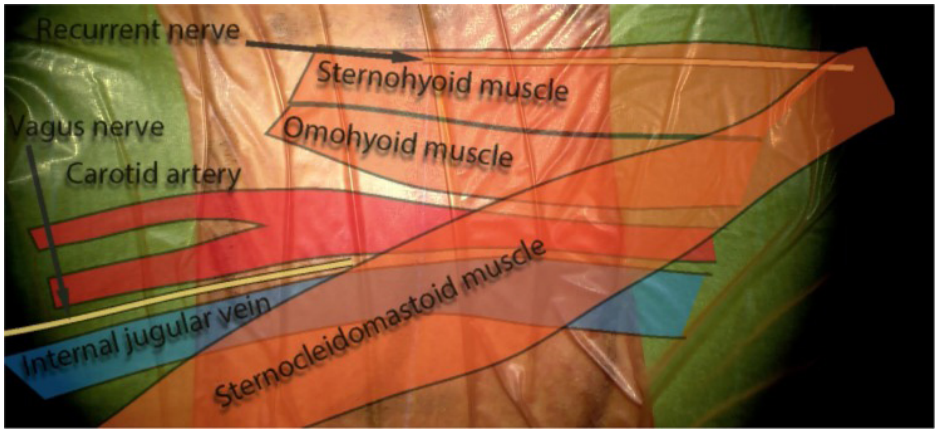

Figure 1: Surgical anatomy of the anterior neck.

Preoperative work-up

Materials required

- Radiolucent table.
- Intraoperative fluoroscopy (C-arm).
- Microscope and/or loupes.
- Vertebral distraction system.
- High speed drill.

Upper airway management for cervical spine surgery is very important for successful anaesthesia. Intubation with an endotrachial tube must be done with minimal movement of the neck to prevent injury of the spinal cord.[1] After general anaesthesia the patient is positioned supine with the head in a light extended position. The utility of neuromonitoring is controversial. Intraoperative neuromonitoring is only performed by the authors, if there is a significant spinal cord compression. Recent research showed that there is no difference in the risk of neurological injury when performing ACDF with or without intraoperative monitoring.[2] After positioning the midline, jugulum and SCM are marked (Figure 2) and the appropriate surgical level is identified using intraoperative fluoroscopy (Figure 3). Fluoroscopic exposure of the cervical vertebrae may be hindered by the shoulders, especially for procedures involving the lower cervical spine. By retracting the shoulders caudally the fluoroscopic exposure of the cervical

spine is increased. In some patients retraction of the shoulders is not sufficient and oblique views might help to improve exposure of the cervical spine. After marking the appropriate level the neck area is cleansed with chloor hexidine and the patient is draped sterile. The authors prefer to enter the disc space from the contralateral side of the cervical disc herniation to have a good view at the exiting nerve root, but ipsilateral or left/right sided approaches are good alternatives.

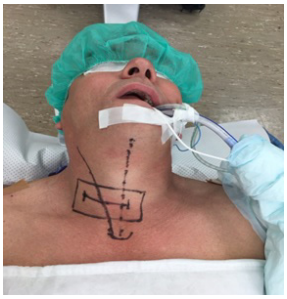

Figure 2: Positioning and marking of the midline, jugulum and sternocleidomastoid muscle.

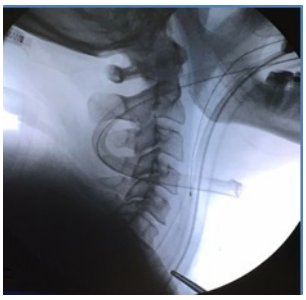

Figure 3: Indentifying the appropriate surgical level with intraoperative fluoroscopy.

Surgical procedure

Please see the Supplemental Digital Content for the accompanying video of the procedure in the references.

Desription of the technique

The level of disc herniation is identified using the C-arm. The angle of approach should be in the extension of the disc space, perpendicular to the anterior longitudinal ligament (ALL).

A 5 cm skin crease incision is made on the right or left side of the neck and the platysma is identified. After transecting the platysma a cleavage plane above the SCM muscle is exposed. Along the medial side of the SCM a tunnel to the spine is created using blunt digital dissection while keeping the carotid sheath ipsilateral. In case of soft tissue resistance sharp dissection with a blunt Metzenbaum scissor is necessary.

The SCM muscle and carotid artery are retracted ipsilateral while the trachea and esophagus are retracted contralateral. Next the prevertebral fascia is dissected in craniocaudal direction using two Kocher clamps with a peanut gauze. After verification of the appropriate level the longus colli muscle is partially detached from the vertebrae with bipolar electrocautery at the disc level. At this point, intraoperative radiographs should be obtained to confirm the appropriate level of the disc herniation (Figure 3).

Self-retaining retractors are placed in four directions, two underneath the left and right longus colli muscle to prevent damage of the sympathic plexus. The other two retractors are placed craniocaudal direction to obtain a safe exposure corridor. At this stage an operating microscope is used. The advantages of using an operative microscope are added magnification and focused lighting to improve the visualization of the surgical field. It also improves the visualization when decompressing the neuroforamen. After the appropriate level has been identified the ALL is incised (Figure 4).

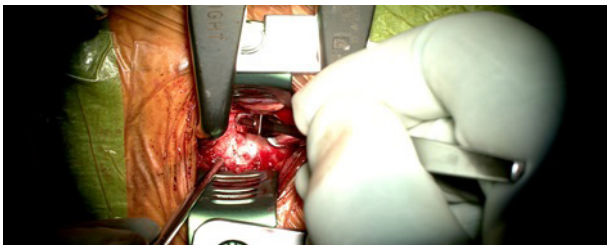

Figure 4: After the appropriate level has been identified the anterior longitudinal ligament is incised.

Under fluoroscopy Caspar distraction pins (usually 14 mm for females and 16 mm for males) are placed in the midline of the upper and lower vertebrae and gentle distraction is applied. The upper and lower endplates are identified and the total disc can be easily detached from the endplates using a small periosteal elevator until the posterior longitudinal ligament (PLL) is identified. Once the PLL is identified a small sharp hook is used to create a corridor to the epidural space. Then a 1 mm Kerrison punch is used to remove the PLL totally and exposing the dura. In case of large posterior osteofytes, a 4 mm side cutting high speed drill is used to remove the osteofytes and the uncinated process. Decompression of the dura is considered appropriate if pulsations of the dura are visible. Next a 2 mm Kerrison punch is used to decompress the neuroforamen. When a blunt tip nerve hook, with a diameter of at least 1 mm, can be introduced into the neuroforamen freely, the decompression is considered enough.

Bleeding from the cervical epidural venous plexus can easily be stopped by injecting saline into the lateral recess.[3] Once the decompression of the neuronal structures is sufficient the distraction is released. At this stage the neuroforamen should still be accessible for the 1 mm nerve hook. If the nerve hook cannot be introduced freely additional decompression of the neuroforamen is necessary (Figure 5).

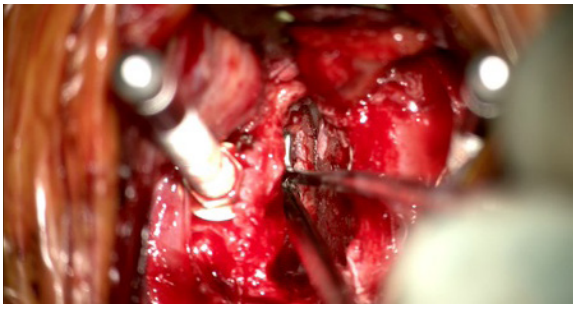

Figure 5: Introduction of the nerve hook into the neuroforamen

Then the distraction screws are removed and the bonewax is used to close the pinholes. Meticulous hemostasis should be performed and rinsing of the wound is performed until no bleeders are observed anymore. The wound is closed in three layers: platysma, subcutis and cutis. The authors prefer to not use a drain routinely.

Indications

Cervical radiculopathy (CR) is a common diagnosis. CR is often self-limiting and can be resolved with non-surgical treatments. The most important symptom is pain, radiating from the neck to the arm. Other symptoms may include sensory loss, loss of motor function or tendon reflex changes in the affected nerve-root distribution.[4] Conservative treatment is recommended for at least two months. When conservative treatment fails and symptoms persist or increase in severity, surgical treatment is considered. Absolute indications for early surgery includes progressive neurological deficit.

Limitations

There are no absolute contra-indications for ACD. A recently conducted study revealed that ACD was expected to give a higher risk for recurrent CR as compared to ACD with fusion (ACDF).[5] Another study concluded that patients who underwent ACD had lower rates of mechanical, device-related complications, lower readmission rates, lower reoperation rates, and reduced total costs than those treated with ACDF.[6] Whether fusion is necessary remains a subject for debate.

How to avoid complications

Optimal knowledge and identification of anatomical structures are important to avoid complication. Intraoperative imaging by fluoroscopy is also recommended.

Specific information to give to the patient about surgery and potential risks

Six hours after surgery, when no complications occur, patients are allowed to mobilize. Patients are usually discharged one day postoperatively. Some patients can experience some neck pain in whom a stiff collar may be helpful. After surgery, work and daily activities should be resumed as soon as possible. The patient should build up his or her activities guided by the pain. Patients are usually scheduled to be monitored 6 weeks after the surgery at the outpatient clinic.

Commonly reported complications are:

- Dysphagia (9.46%) due to esophageal retraction and intubation.[7]
- Vocal cord paralyses (2.3% - 24.2%) due to injury of the recurrent laryngeal nerve.[8]
- Incidental dural tears leading to cerebrospinal fluid leak (1.3%).[9]
- Hoarseness (1.2%) due to injury of the recurrent laryngeal nerve.[9]
- Airway compromisation due to laryngopharyngeal edema (2.8%-6.1%) can cause difficulty with breathing and talking, dyspnea, cyanosis and inspiratory stridor.[10]
- C5 palsy (3.3%).[11]

The severity of most of these complications decreases over time. Other complications are esophageal perforation, wound infection, injury of the vertebral artery, and spinal cord and nerve root injury. Rare complications include postoperative hematoma and laryngopharyngeal edema leading to airway compromise.[7] Damage to the sympathetic chain may cause ipsilateral miosis, ptosis and anhidrosis, also know as Horner's syndrome.

Key points

- With an adequate clinical indication and surgery performed properly, the results of this procedure are excellent.
- Routine use of intraoperative neuromonitoring is not recommended by the authors.
- Surgery from the contralateral side provides a better view of the neuroforamen.
- A false cleavage plane complicates the procedure enormously.
- Placing the tissue retractor underneath the longus colli muscle is key to preventing damage to the sympathetic chain.
- After a skin incision has been made in the front of the neck, only one thin vestigial muscle needs to be cut, after which the anatomic planes can be followed right down to the spine. The limited amount of muscle division or dissection helps to limit postoperative pain following the spinal surgery.
- With meticulous hemostasis a wound drain is not necessary.
- Appropriate dissection is associated with less than 50 ml blood loss.
- When performed properly, ACD is simply more costeffective compared to ACDF.
- Transient dysphagia is the most commonly seen complication.

References

1. Farag E. Airway management for cervical spine surgery. Best Pract Res Clin anaesthesiol. 2016;30:13-25.
2. Ajiboye RM, Zoller SD, Sharma A, et al. Intraoperative Neuromonitoring for Anterior Cervical Spine Surgery: What is the Evidence? Spine (Phila Pa 1976). 2016.
3. Menovsky T, De Ridder D. Simple intraoperative technique for hemostasis of cervical venous bleeding. Neurosurgery. 2008;62:ONS442-4; discussion ONS4.
4. Carette S, Fehlings MG. Clinical practice. Cervical radiculopathy. N Engl J Med. 2005;353:392-9.
5. de Rooij JD, Gadjradj PS, Huygen FJ, Luijsterburg PA, Harhangi BS. Management of Symptomatic Cervical Disk Herniation: a Survey among Dutch Neurosurgeons. Spine (Phila Pa 1976). 2016.
6. Radcliff K, Zigler J, Zigler J. Costs of cervical disc replacement versus anterior cervical discectomy and fusion for treatment of single-level cervical disc disease: an analysis of the Blue Health Intelligence database for acute and long-term costs and complications. Spine (Phila Pa 1976). 2015;40:521-9.
7. Zhong ZM, Li M, Han ZM, et al. Does cervical disc arthroplasty have lower incidence of dysphagia than anterior cervical discectomy and fusion? A meta-analysis. Clin Neurol Neurosurg. 2016;146:45-51.
8. Tan TP, Govindarajulu AP, Massicotte EM, Venkatraghavan L. Vocal cord palsy after anterior cervical spine surgery: a qualitative systematic review. Spine J. 2014;14:1332-42.
9. Nanda A, Sharma M, Sonig A, Ambekar S, Bollam P. Surgical complications of anterior cervical diskectomy and fusion for cervical degenerative disk disease: a single surgeon's experience of 1,576 patients. World Neurosurg. 2014;82:1380-7.
10. Palumbo MA, Aidlen JP, Daniels AH, Bianco A, Caiati JM. Airway compromise due to laryngopharyngeal edema after anterior cervical spine surgery. J Clin Anesth. 2013;25:66-72.
11. Shou F, Li Z, Wang H, Yan C, Liu Q, Xiao C. Prevalence of C5 nerve root palsy after cervical decompressive surgery: a meta-analysis. Eur Spine J. 2015;24:2724-34.

QR-code Surgical procedure:

Chapter six

MANAGEMENT OF A CERVICAL DISC HERNIATION: A SURVEY AMONG DUTCH NEUROSURGEONS

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Abstract

Study Design
A questionnaire survey.

Objective
To assess the preferred surgical technique, the optimal timing of surgery, and the expectations of different surgical techniques of neurosurgeons in the Netherlands, regarding patients with a cervical disc herniation (CDH).

Summary of Background Data
To treat CDH, multiple surgical techniques are performed. Due to the lack of consensus, the daily routine management may vary.

Methods
All 134 neurosurgeons of the Dutch Association of Neurosurgery were sent a survey, evaluating the operative management as well as the attitude towards different surgical treatments for CDH.

Results
Ninety-six (74.4%) of the neurosurgeons treating CDH completed the survey. Anterior cervical discectomy with fusion (ACDF) was the standard procedure for the majority of neurosurgeons (76.3%). ACDF was expected to have the highest effectiveness on arm pain, yet also a higher risk for complications as compared with anterior cervical discectomy (ACD). Approximately, 47.9% of the surgeons regarded a minimal duration of 8 to 12 weeks of radicular arm pain before deciding to perform surgery. Regarding the risk of recurrent CDH, dorsal cervical foraminotomy (DCF) was expected to give the highest risk, whereas ACDF the lowest.

Conclusion
Despite the lack of solid evidence in favor for ACDF this survey showed that ACDF is the preferred technique to treat cervical radiculopathy. A minimum duration of 8 to 12 weeks of radicular arm pain was considered the optimal timing to perform surgery for CDH by the majority of the neurosurgeons. Whether to fuse or not remains a controversial subject in degenerative spinal surgery. This study emphasizes the need of high-quality evidence on the optimal surgical management of CDH.

Introduction

Symptomatic cervical disc herniation (CDH) is a common diagnosis and epidemiological data on symptomatic CDH are scarce. In the United States each year 83.2 per 100,000 patients are affected[1] and recently an incidence was found of 1.79 per 1000 person-years.[2] CDH is often associated with degenerative disc disease (DDD) and may cause significant pain, instability, radiculopathy, myelopathy, or a combination of symptoms.[1,2] The term DDD is used to describe normal changes in the spinal disc as people age.[3] DDD may include desiccation, fibrosis, narrowing of the disc space, diffuse bulging of the annulus beyond the disc space, annular fissures, mucinous degeneration of the annulus, and sclerosis of the end plates.[4] DDD can also lead to herniation of the nucleus into the neuroforamen or spinal canal. The loss of disc height may also incline instability that is compensated by the formation of osteophytes narrowing the neuroforamen even further. Eventually symptoms may arise because of a CDH with compression of the rootlet or spinal cord.[2] When conservative treatment for CDH fails, surgical treatment may be considered.[3]

The main goals of surgical treatment are to remove pressure from the nerves, restore the alignment of the vertebrae, to stabilize the spine,[3] and to prevent progression of neurological deficit in case of myelopathy.[5] A frequently performed surgical approach is the anterior discectomy which can be performed either with fusion (ACDF) or without fusion (ACD).[3] Another approach is the dorsal cervical foraminotomy (DCF). This procedure allows osseous decompression of the nerve root and subsequent extraction of sequestered disc material that laterally compresses the nerve root with or without spinal cord compression.[6] Because of conflicting data, there is no consensus which technique has superior clinical outcomes.[3,5,7,8] The surgeon will decide to perform either a dorsal or ventral approach to relieve the pressure upon the nerve root. This decision is largely based on individual preferences and on surgical experience rather than on evidence-based recommendations.[6,9] Many surgeons consider a ventral approach when the herniated disc crosses the midline of the vertebral corpus whereas other surgeons prefer the dorsal approach in patients with only soft sequestration.[6]

The purpose of the current study was to give an overview of the current management of CDH by neurosurgeons in the Netherlands and to address the preferred surgical technique, the optimal timing for surgery, and the expectations of different surgical techniques.

Methods

In 2015, all 134 clinically active surgeons of the Dutch Association of Neurosurgery were asked to fill in a survey. Residents, surgeons not performing surgery for CDH and retired neurosurgeons were excluded from this study. Nonresponders were sent a reminder by mail after 1 and 2 months. The survey was developed by the authors of this article, based on the Dutch Guideline on the treatment of cervical radiculopathy caused by CDH.[10] The initial survey was first tested among neurosurgeons of the Erasmus MC: University Medical Center, Rotterdam after which adjustments for the final version were made, see QR-code in references.

The survey consisted of 16 questions addressing various aspects of surgical and postsurgical treatment of symptomatic CDH: (i) the surgeon's demographics as sex and the years of clinical practice; (ii) the characteristics of the standard surgical procedure as the technique, the side of performing surgery, the use of magnification, and the extent of disc removal; (iii) the optimal timing for surgery in patients with radiculopathy; (iv) the expected effects of three surgical techniques on clinical outcomes as radiating arm pain, neck pain, the risk of recurrent radiculopathy, and the expected risk for complications; (v) the occurrence of various complications, and (vi) the postoperative management such as the prescription of physiotherapy and the timing of recommending resumption of work and daily activities. All data were analyzed using descriptive statistics using SPSS software version 21.0 for Windows. Categorical data were compared by χ^2analysis, whereas a $P < 0.05$ was considered as statistically significant. Frequencies are depicted as percentages of valid responses whereas missing answers of duplicate answers were excluded from analysis.

Results

Surgeon's Demographics

Hundred-one surgeons (75.4%) of the 134 surgeons replied. Five respondents stated that they did not perform surgery for CDH and were therefore excluded, leaving 96 respondents (74.4%) from 129 neurosurgeons for the analysis. Approximately, 88.0% of the responders were males and 12.0% were females with a median clinical experience of 14 years (interquartile range, IQR, 14) (Table 1).

Characteristic	Number of valid responders (%)
Sex	
Male	81 (88.0)
Side of performing surgery	
Ipsilateral	2 (2.1)
Contralateral	24 (25.0)
Always from left side	4 (4.2)
Always from right side	66 (68.8)
Use of magnification during actual discectomy	
No use	1 (1.1)
Loupes	5 (5.3)
Microscope	68 (71.6)
Microscope and loupes	21 (22.1)
Extent of disc removal	
only the sequester (in case of sequestration)	2 (2.1)
small extent of the disc unilaterally	0 (0)
large extent of the disc unilaterally	9 (9.4)
complete disc unilaterally including drilling of the uncinated process	7(7.3)
large extent of the disc bilaterally	45 (46.9)
complete disc bilaterally including drilling of the uncinated process	33 (34.4)
Missing values ranged from 1.1% to 4.2%	

Table 1: Baseline characteristics and surgical characteristics of the responding neurosurgeons (n=96).

Characteristics of Standard Surgical Procedure

In the last 5 years, the majority of the neurosurgeons (58.3%) performed more than 50 cervical disc surgeries, whereas 26.0% performed 21 to 50 cervical disc surgeries, and 15.6% performed less than 21 procedures. The most frequently applied technique was ACDF (76.3%), followed by ACD (19.4%). Only 4.3% of the neurosurgeons applied DCF and percutaneous minimal invasive foraminotomy was not performed among the responders. Surgeons performing more surgeries for CDH the last 5 year differed

statistically significant (P = 0.009) in the standard procedure used for discectomy, as compared with surgeons performing less procedures (Figure 1). Regarding the extent of the disc removal, more than 80% of the surgeons removed either a large extent of the disc or the complete disc bilaterally. The remaining 18.8% of the respondents removed either the sequester or extents of the disc unilaterally (Table 1).

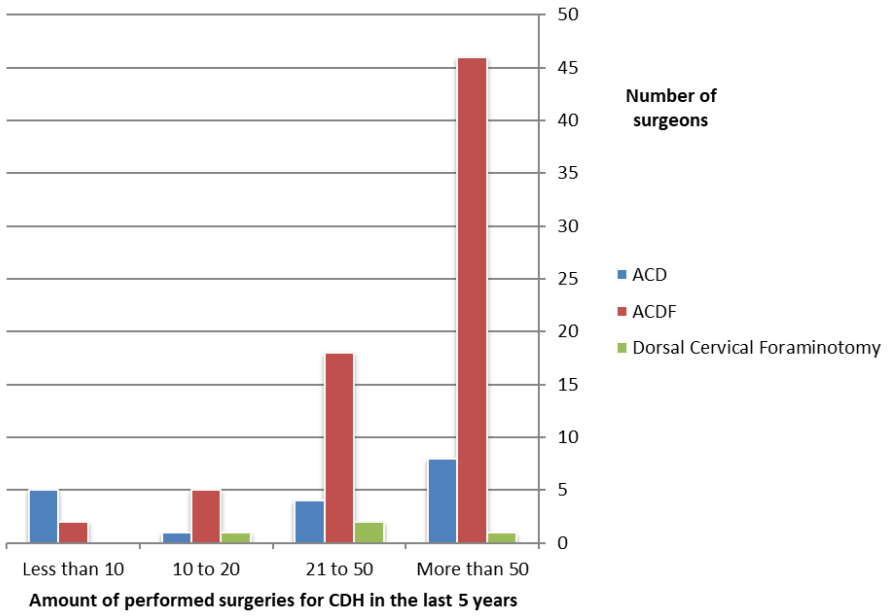

Figure 1: Amount of performed surgeries for CDH in the last 5 years compared with standard surgical procedure.

Optimal Timing of Surgery in Patients With Radiculopathy

The majority (47.9%) of the neurosurgeons considered a minimum of 8 to 12 weeks of radiculopathy before indicating surgery. More than a fifth of the surgeons regarded at least 12 weeks of radiculopathy as a minimum, whereas more than 30% performed surgery within 2 months of radiculopathy (Table 2). In case of motor deficits, only a total paralysis was an indication for surgery within 24 hours by two-third of the surgeons. Surgery for patients with unsustainable pain was regarded as the least urgent and the majority stated that in this case surgery could be performed after more than 1 week (Table 2).

Symptoms	Percentage of valid responders (%)			
Minimum duration of radicular arm pain to decide to perform surgery				
< 2weeks	1.0			
2-4 weeks	3.1			
>4-8 weeks	27.1			
>8-12 weeks	47.9			
>12 weeks	20.8			
Optimal timing for CDH surgery	**Never**	**< 24 hours**	**< 1 week**	**>1 week**
Total paralysis	10.8	67.5	15.7	6.0
Paresis grades 1-3	3.6	34.9	49.4	12.0
Paresis grade 4	2.4	11.8	38.8	47.1
Progressive motor loss	1.3	32.5	51.3	15.0
Unsustainable pain(VAS>6)	0.0	1.2	33.3	65.5

Missing values ranged from 0% to 16.7%.
All results are presented as percentages.
CDH: Cervical Disc Herniation.

Table 2: Surgeons' opinions of the optimal timing of surgery.

Expectations of Clinical Outcomes for Various Surgical Techniques

Out of the three techniques, ACDF was expected to be the most effective on arm pain on both the short and long term by 57.4% and 52.7% of the respondents, respectively (Table 3). DCF was expected to be the least effective with 24.7% and 19.1% of the respondents expecting it to give the most arm pain on the short- and long-term respectively. When concerning postoperative neck pain, more than 40% of the surgeons expected DCF to give the most pain on the short-term, whereas ACDF was expected to give the least neck pain by 30.0%. Risks of recurrent radiculopathy on both the short- and long-term was expected to be the highest after DCF (by 56.2% and 57.2% of the respondents, respectively) and the lowest after ACDF (by 75.3% and 76.9%, respectively). Almost 40% of the surgeons expected ACD to give the lowest risk for complications, whereas DCF (19.8%) and ACDF (15.2%) were expected to give the highest risk.

Techniques		Anterior Cervical Discectomy	Anterior Cervical Discectomy with Fusion	Dorsal Cervical Foraminotomy
Arm pain (short-term)	Most	12.0	11.7	24.7
	Neutral	62.0	30.9	58.1
	Least	26.1	57.4	17.2
Arm pain (long-term)	Most	11.2	14.3	19.1
	Neutral	64.0	33.0	58.4
	Least	24.7	52.7	22.5
Neck pain (short-term)	Most	12.4	13.3	41.8
	Neutral	64.0	56.7	45.1
	Least	23.6	30.0	13.2
Risk of recurrent CR (short-term)	Most	10.2	3.2	56.2
	Neutral	52.3	21.5	30.3
	Least	37.5	75.3	13.5
Risk of recurrent CR (long-term)	Most	4.5	1.1	57.5
	Neutral	62.5	22.0	33.3
	Least	33.0	76.9	9.2
Expected risk for complications	Most	3.4	15.2	19.8
	Neutral	57.3	55.4	46.2
	Least	39.3	29.3	34.1

CR: cervical radiculopathy.
All results are presented as percentages.
Missing values ranged from 1.9% to 8.7%.

Table 3: Expectations for surgical outcome of the 96 neurosurgeons.

Occurrence of Various Complications in Practice

The most frequently observed complications were swallowing disorders with 18.1% and hoarseness with 4.2% of the surgeons reporting a frequency of more than 10%, respectively (Table 4). Injury of the vertebral artery, perforation of the esophagus and Horner's syndrome were the rarest complications with 87.4%, 73.3%, and 53.2% of the neurosurgeons, respectively, reporting to not have seen these complications in practice at all.

	0 out of 100 cases	1 out of 1000 cases	1 out of 100 cases	Less than 10 out of 100 cases	More than 10 out of 100 cases
Hoarseness	5.3	23.2	41.1	26.3	4.2
Swallowing disorders	4.3	12.8	22.3	42.6	18.1
Horner`s syndrome	53.2	31.9	10.6	4.3	0
Leakage of cerebrospinal fluid	41.1	43.2	14.7	1.1	0
Increased neurological deficits	10.5	31.6	42.1	15.8	0
Esophageal perforation	73.7	23.2	2.1	1.1	0
Vertebral artery injury	87.4	10.5	2.1	0	0
Wound infection	21.5	36.6	31.2	10.8	0

All results are presented as percentages.
Missing values ranged from 1% to 3.1%.

Table 4: Reported occurrence of various complications in practice.

Postoperative Management

Physiotherapy is never prescribed postoperatively by 50.5% of the neurosurgeons, whereas 7.4% reported to always prescribe it. At least 4 weeks after surgery, most surgeons allowed resumption of work and daily activities, whereas 5.6% allowed it directly after discharge (Figure 2).

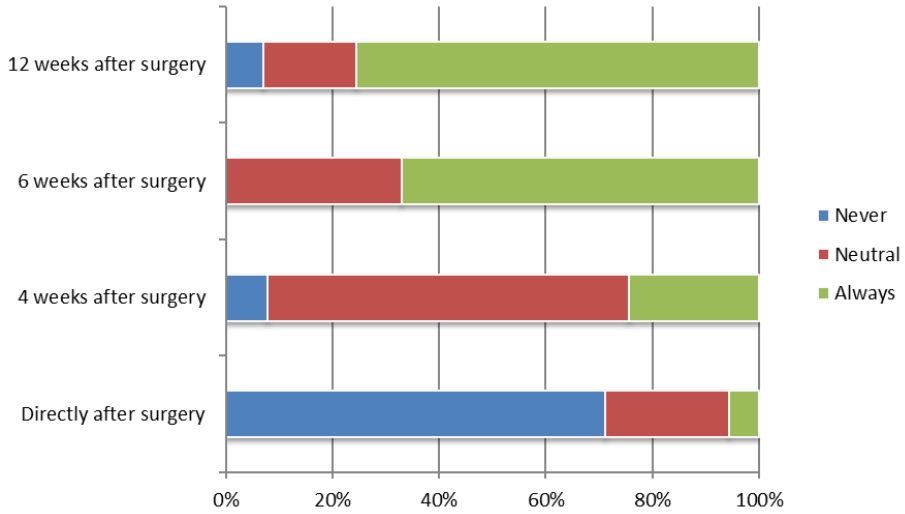

Figure 2: Recommendation of resumption of work and daily activities postoperative.

Discussion

This study presents the current management of CDH by neurosurgeons in the Netherlands. Most of the respondents performed more than 50 procedures during the last 5 years. ACDF was the far most reported preferred surgical technique, which is in agreement with the Evidence-Based Clinical Guidelines from the North American Spine Society.[11] Remarkable is that for the surgeons who performed less than 10 procedures in the last 5 years, ACD was performed more frequently than ACDF.

Small variations between the respondents, regarding the optimal timing of surgery in patients with radiculopathy were observed. Most of the respondents decided to operate on patients after 8 to 12 weeks of radicular arm pain. To our knowledge, there are no randomized controlled trials regarding the optimal timing of surgery in patients with cervical radiculopathy due to CDH. However, conservative treatment is recommended for at least 2 months according to Dutch guidelines. When conservative treatment fails and symptoms persist or increase in severity, surgical treatment is considered.[10] The major advantage of early surgery is fast pain relief, but the long term overall outcome may be similar to conservative treatment.[12–14] There are only a few studies describing the optimal timing of surgery in patients with lumbar disc herniation. In a randomized controlled trial, Peul *et al*[15] assigned patients with lumbar disc herniation to conservative treatment or early surgery. After 1 year of follow up, clinical outcomes were similar for patients who underwent early surgery compared with those assigned to prolonged conservative treatment. The pain relief and self-perceived recovery were faster for those assigned to early surgery.[15] Dubuisson *et al*[16] performed a retrospective study on 24 patients, who underwent surgery for paralyzing lumbar disc herniation. In this study, delaying surgery did not influence the degree recovery of motor deficit. The authors refer to a relative consensus existing among spine surgeons for paralyzing lumbar disc herniation to operate as soon as possible.[16]

Whether to fuse or not remains a controversial subject in degenerative spinal surgery. Bambakidis *et al*[17] performed a literature review and aimed to establish absolute and relative criteria to indicate fusion in degenerative spinal surgery. They state that although they think that anterior fusion after discectomy is controversial, they do recommend fusion because of the risk of postoperative kyphosis, persistent neck pain, and compression of the nerve rootlet. In a similar fashion, the indication for fusion of the lumbar spine after decompression with Grade I spondylolisthesis was deemed controversial. However, recently a large randomized controlled trial[18] was published that showed that fusion in addition to decompression did not result in better clinical outcomes after 2 or 5 years of follow up. However, patients who underwent fusion had longer durations of surgery, higher amounts of estimated blood loss, and longer rate of hospitalization and higher costs of surgery, data suggesting a paradigm shift in the role of fusion in degenerative spinal surgery.

Of the 92 surgeons who either performed ACD or ACDF as a standard procedure, almost 80% performed ACDF. ACDF was expected to give the least arm pain and the lowest risk of recurrent radiculopathy on both the short- and long-term. However, at the same time ACDF was expected to give a higher risk for complications then ACD. A possible advantage of fusion is the reduction of the risk of subsidence, however possible disadvantages are the accompanying risk for adjacent segment disease, dislocation, loosening, or breakage of screws and plates and higher costs of surgery.[7,19–22] Xie and Hurlbert[8] performed a prospective study, randomizing 45 patients between ACD or ACDF with or without instrumented fusion. After 2 years of follow up, there were no significant differences between the three groups regarding clinical outcomes as pain and quality of life. When comparing radiographic outcomes between the three groups, the rate of nonunion and the rate of loss of lordosis in the ACD group was significantly higher than the ACDF groups after both 3 months and 2 years. However, there was no significant difference in symptomatic adjacent segment disease between the 3 groups. Radcliff *et al*[23] recently published a retrospective analysis of 6635 patients, who underwent ACDF and 327 patients who were treated with ACD. They found that ACDF had a higher incidence of postoperative complications than ACD. ACDF had a significant increased incidence of mechanical (device-related) complications, medical complications, and complications during reoperation.[23] The cumulative 36-month incidence of reoperation in ACDF patients (10.5%) was almost twice of that of ACD patients (5.7%) and of the patients that underwent reoperation, there was also an increase in the percentage of medical comorbidities in ACDF patients (25.65%) *versus* ACD patients (10%).[23] The use of cages and plates to increase the progress of fusion of ACDF is still subject of debate.[7] The purpose of an anterior instrumentation is to maintain cervical lordosis, avoid kyphotic deformity, and prevent motion of the spine so that arthrodesis can occur in a more stable environment.[7]

Swallowing disorders and hoarseness were the most observed complications among the Dutch neurosurgeons. Nanda *et al*[24] performed a retrospective study of the surgical complications of ACD and ACDF for cervical DDD in 1576 patients. The most commonly reported complications were dysphagia (3.3%), followed by incidental durotomy and cerebrospinal fluid leak (1.3%) and hoarseness (1.2%).[24] Other studies reported incidences of dysphagia, ranging from 8% to 88% in the first 3 months after cervical spine surgery, including both anterior and posterior techniques.[25–28] However the incidence and severity of most of these cases decreases over time. In a large retrospective study of 1895 patients undergoing ACDF, the incidence of vocal cord paralysis (0.47% and 0.16% after 3 months and 9 months, respectively) was similar to our findings. Their study showed that patients who did not recover from the paralysis after 9 months, still didn't recover 3 years after surgery.[29]

The majority of the neurosurgeons did not prescribe physiotherapy postoperatively. The North American Spine Society and the Royal Dutch Society of Physiotherapy do

not provide recommendations on prescribing physiotherapy postoperatively. Evidence for recommendations regarding resumption of work and daily activities after surgery is still lacking. In this survey, majority of the respondents allowed their patients to resume to work and daily activities after 12 weeks. Oosterhuis *et al*[30] performed a systematic review investigating rehabilitation after surgery for lumbar disc herniation. They concluded, despite the absence of high or moderate quality evidence, that exercise therapy postoperatively may result into a faster decrease in pain and disability, compared with no treatment. This might also be applicable to patients recovering from surgery for CDH.

Strength of this study is the high response rate among neurosurgeons performing CDH surgery, providing a good representation of the management of CDH in the Netherlands. However, the current study has also its limitations. A limitation of this study is global generalizability, as the survey was only conducted in the Netherlands. However, it is plausible that this variation may also be present worldwide because there is a lack of consensus recording to the different treatment modalities. Another limitation is that we did not include orthopedic surgeons performing surgery for CDH. However, this limitation is negligible since most surgeries for CDH are performed by neurosurgeons in the Netherlands.

Conclusion

Despite the lack of solid evidence in favor for ACDF, this survey showed that ACDF is the preferred technique to treat cervical radiculopathy. A minimum duration of 8 to 12 weeks of radicular arm pain was considered the optimal timing to perform surgery. Whether to fuse or not remains a controversial subject in degenerative spinal surgery. This study emphasizes the need of high-quality evidence on the optimal surgical management of CDH.

Key points

- ACDF is the most frequently performed procedure for cervical disc herniation in the Netherlands.
- A minimum duration of 8 to 12 weeks of radicular arm pain was considered to be the optimal timing to perform surgery by most of the neurosurgeons.
- The majority of the surgeons expected ACDF to have the highest effectiveness on arm pain, to give the lowest neck pain and to give the lowest risk for recurrent radiculopathy.

References

1. Radhakrishnan K, Litchy WJ, O'Fallon WM, et al. Epidemiology of cervical radiculopathy. A population-based study from Rochester, Minnesota, 1976 through 1990. Brain 1994; 117:325–335.
2. Schoenfeld AJ, George AA, Bader JO, et al. Incidence and epidemiology of cervical radiculopathy in the United States military: 2000 to 2009. J Spinal Disord Tech 2012; 25:17–22.
3. Jacobs W, Willems PC, Kruyt M, et al. Systematic review of anterior interbody fusion techniques for single- and double-level cervical degenerative disc disease. Spine (Phila Pa 1976) 2011; 36:E950–E960.
4. Fardon DF, Williams AL, Dohring EJ, et al. Lumbar disc nomenclature: version 2.0: Recommendations of the combined task forces of the North American Spine Society, the American Society of Spine Radiology and the American Society of Neuroradiology. Spine J 2014; 14:2525–2545.
5. Boselie TF, Willems PC, van Mameren H, et al. Arthroplasty versus fusion in single-level cervical degenerative disc disease: a Cochrane review. Spine (Phila Pa 1976) 2013; 38:E1096–E1107.
6. Schebesch KM, Albert R, Schodel P, et al. A single neurosurgical center's experience of the resolution of cervical radiculopathy after dorsal foraminotomy and ventral discectomy. J Clin Neurosci 2011; 18:1090–1092.
7. Nabhan A, Pape D, Pitzen T, et al. Radiographic analysis of fusion progression following one-level cervical fusion with or without plate fixation. Zentralbl Neurochir 2007; 68:133–138.
8. Xie JC, Hurlbert RJ. Discectomy versus discectomy with fusion versus discectomy with fusion and instrumentation: a prospective randomized study. Neurosurgery 2007; 61:107–116. discussion 16-17.
9. Irwin ZN, Hilibrand A, Gustavel M, et al. Variation in surgical decision making for degenerative spinal disorders. Part II: cervical spine. Spine (Phila Pa 1976) 2005; 30:2214–2219.
10. Dutch Society for Neurology: [Guideline Cervical Radicular Syndrome.] Utrecht: Quality Institute for Health Care CBO, 2008 (Dutch): 1–99.
11. NASS NASS. Diagnosis and Treatment of Cervical Radiculopathy from Degenerative Disorders, 2010. https://www.spine.org/Documents/ResearchClinicalCare/Guidelines/CervicalRadiculopathy.pdf.
12. Gebremariam L, Koes BW, Peul WC, et al. Evaluation of treatment effectiveness for the herniated cervical disc: a systematic review. Spine (Phila Pa 1976) 2012; 37:E109–E118.
13. Nikolaidis I, Fouyas IP, Sandercock PA, et al. Surgery for cervical radiculopathy or myelopathy. Cochrane Database Syst Rev 2010; CD001466.
14. van Middelkoop M, Rubinstein SM, Ostelo R, et al. Surgery versus conservative care for neck pain: a systematic review. Eur Spine J 2013; 22:87–95.
15. Peul WC, van Houwelingen HC, van den Hout WB, et al. Surgery versus prolonged conservative treatment for sciatica. N Engl J Med 2007; 356:2245–2256.
16. Dubuisson A, Borlon S, Scholtes F, et al. [Paralysing lumbar disc herniation: a surgical emergency? Reflexion about a series of 24 patients and literature data]La hernie discale lombaire paralysante: une urgence chirurgicale ? Reflexion a propos d'une serie de 24 patients et des donnees de la litterature. Neurochirurgie 2013; 59:64–68.
17. Bambakidis NC, Feiz-Erfan I, Klopfenstein JD, et al. Indications for surgical fusion of the cervical and lumbar motion segment. Spine (Phila Pa 1976) 2005; 30:S2–6.
18. Forsth P, Olafsson G, Carlsson T, et al. A randomized, controlled trial of fusion surgery for lumbar spinal stenosis. N Engl J Med 2016; 374:1413–1423.
19. Pompili A, Canitano S, Caroli F, et al. Asymptomatic esophageal perforation caused by late screw migration after anterior cervical plating: report of a case and review of relevant literature. Spine (Phila Pa 1976) 2002; 27:E499–E502.
20. Yang B, Li H, Zhang T, et al. The incidence of adjacent segment degeneration after cervical disc arthroplasty (CDA): a meta analysis of randomized controlled trials. PLoS One 2012; 7:e35032.

21. Lund T, Oxland TR. Adjacent level disk disease-is it really a fusion disease? Orthop Clin N Am 2011; 42:521–529.
22. Oktenoglu T, Cosar M, Ozer AF, et al. Anterior cervical microdiscectomy with or without fusion. J Spinal Disord Tech 2007; 20:361–368.
23. Radcliff K, Zigler J, Zigler J. Costs of cervical disc replacement versus anterior cervical discectomy and fusion for treatment of single-level cervical disc disease: an analysis of the Blue Health Intelligence database for acute and long-term costs and complications. Spine (Phila Pa 1976) 2015; 40:521–529.
24. Nanda A, Sharma M, Sonig A, et al. Surgical complications of anterior cervical diskectomy and fusion for cervical degenerative disk disease: a single surgeon's experience of 1576 patients. World Neurosurg 2014; 82:1380–1387.
25. Smith-Hammond CA, New KC, Pietrobon R, et al. Prospective analysis of incidence and risk factors of dysphagia in spine surgery patients: comparison of anterior cervical, posterior cervical, and lumbar procedures. Spine (Phila Pa 1976) 2004; 29:1441–1446.
26. Bazaz R, Lee MJ, Yoo JU. Incidence of dysphagia after anterior cervical spine surgery: a prospective study. Spine (Phila Pa 1976) 2002; 27:2453–2458.
27. Kalb S, Reis MT, Cowperthwaite MC, et al. Dysphagia after anterior cervical spine surgery: incidence and risk factors. World Neurosurg 2012; 77:183–187.
28. Rihn JA, Kane J, Albert TJ, et al. What is the incidence and severity of dysphagia after anterior cervical surgery? Clin Orthop Relat R 2011; 469:658–665.
29. Chen CC, Huang YC, Lee ST, et al. Long-term result of vocal cord paralysis after anterior cervical disectomy. European Spine Journal 2014; 23:622–626.
30. Oosterhuis T, Costa LO, Maher CG, et al. Rehabilitation after lumbar disc surgery. Cochrane Database Syst Rev 2014; 3:CD003007.

QR-code survey:

Part three

Nucleoplasty trial and the retrospective cohort study

Chapter seven

THE EFFECT OF PERCUTANEOUS NUCELOPLASTY VERSUS ANTERIOR DISCECTOMY IN PATIENTS WITH CERVICAL RADICULAR PAIN DUE TO A SINGLE CONTAINED SOFT-DISC HERNIATION: A RANDOMIZED CONTROLLED TRIAL

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Abstract

Background

Cervical radicular pain (CRP) is a common problem in the adult population. When conservative treatment fails and the severe pain persist, surgical treatment is considered. However, surgery is associated with some serious risks. To reduce these risks, new minimally invasive techniques have been developed, such as percutaneous nucleoplasty. Several studies have shown that percutaneous nucleoplasty is a safe and effective technique for the treatment of CRP, but until now no randomized controlled trials have been conducted that compare percutaneous cervical nucleoplasty (PCN) to anterior cervical discectomy (ACD) in patients with a single-level contained soft-disc herniation.

Objectives

To compare the effects of PCN and ACD in a group of patients with CRP caused by a single- level contained soft-disc herniation.

Study Design

A randomized, controlled, multi-center trial.
Setting: Medical University Center and local hospitals.

Methods

Forty-eight patients with CRP as a result of a single-level contained soft-disc herniation were randomized to one of the following 2 treatments: PCN or ACD. The primary outcome measure was arm pain intensity, measured with a Visual Analog Scale (VAS). Secondary outcomes were arm pain intensity during heavy effort, neck pain, global perceived effect, Neck Disability Index (NDI), and the patients' general health (36 Item Short Form Generated Health Survey [SF-36]). All parameters were measured at baseline (T0), 3 months after intervention (T2), and one year after intervention (T3). One week after the intervention (T1), an intermediate assessment of arm pain, arm pain during heavy effort, neck pain, satisfaction, and improvement were performed.

Results

At 3 months, the intention to treat analyses revealed a statistical significant interaction between the groups on the primary outcome, arm pain intensity, and on the secondary outcome of the SF-36 item pain, in favor of the ACD group. On the other secondary outcomes, no statistical significant differences were found between the groups over time. At 12 months, there was a trend for more improvement of arm pain in favor of the ACD group and no statistical interactions were found on the secondary outcomes.

Limitations

Firstly, the inclusion by the participating hospitals was limited. Secondly, the trial was ended before reaching the required sample size. Thirdly, at baseline, after the inclusion by the neurosurgeon, 13 patients scored less than 50.0 mm on the VAS. Fourthly, the withdrawal of the physiotherapy (PT) group and finally, the patients and interventionists could not be blinded for the treatment.

Conclusions

At 3 months, the ACD group performed significantly better on arm pain reduction than the PCN group in patients with CRP as a result of a single-level contained soft-disc hernia. However, the clinical relevancy of this treatment effect can be debated. For all parameters, after one year, no significant differences between the groups were found. When it comes to the longer-term effectiveness, we conclude that PCN can be a good alternative for ACD.

Key words

Anterior cervical discectomy, cervical radicular pain, minimal invasive treatment, percutaneous cervical nucleoplasty, randomized controlled trial, single-level contained soft-disc hernia.

Introduction

Cervical radicular pain (CRP) is a common problem in the adult population.[1,2] Each year 83.2 patients in a population of 100.000 persons are affected.[3] CRP usually presents with pain in the neck, then radiates into the arm and fingers.[2,4] In the majority of patients, the natural course of CRP is favorable.[2,3,5] However, when conservative treatment (CT), such as anti-inflammatory medications, immobilization, physiotherapy (PT), and epidural steroid injections [2,6,7], fails and the severe pain persists, surgical treatment is considered.[7] The most common surgical technique for treating CRP due to a disc herniation, involves the removal of the herniated disc, typically followed by fusion of the 2 adjacent vertebral bodies.[8,9] We prefer the ACD technique, which is an accepted surgical treatment for patients with CRP.[10-12] But nowadays, the ACD with fusion technique (ACDF) is seen as the gold standard.[12,13] The rationale of ACDF is to maintain cervical lordosis, to avoid kyphotic spine deformation, and to prevent motion of the cervical spine so that arthrodesis can occur in a more stable environment.[14] However, solid proof for the superiority of ACDF is lacking and 2 recent randomized trials comparing ACD to ACDF with intervertebral cage or with disk prosthesis in patients with CRP, show similar results on neck and arm pain, disability due to neck pain, and quality of life.[10,12] Surgery is also associated with some rare, but serious complications, such as oesophageal injury, postoperative hematoma, mortality[8,15,16], and adjacent level disease.[10,12,17] To further reduce these risks, new minimally invasive treatments for vertebral disc diseases have been developed in the last 3 decades. One such technique is percutaneous cervical nucleoplasty (PCN), it uses coblation technology for ablating and coagulating soft-tissue of the herniated disc.[18] This causes disc decompression, reducing intradiscal pressure, and hence relieves the internal forces that cause irritation of the adjacent nerve root.[18,19] It induces the down-regulation of local inflammatory mediators, reduces disc size, and initiates the healing process, all contributing to a reduction of radicular pain.[20] Several studies have shown that PCN is a safe and effective technique with good results (i.e., 60 to 85 percent of patients have good to excellent patient satisfaction after a PCN).[1,21-25] The procedure can be performed under local anesthesia. This also reduces the risk of trauma and provides shorter convalescence[21,26] with no reported neurological complications of the procedure itself .[27,28] The objective of this randomized controlled trial (RCT) is to compare the effects of PCN and ACD in a group of patients with CRP caused by a single-level contained soft-disc herniation.

Methods

Between April 2012 and March 2018, a prospective, randomized multi-center trial was conducted among patients with CRP as a result of a single-level contained soft-disc hernia. The protocol was approved by the Medical Research Ethics Committee (MREC) of the Erasmus University Medical Center Rotterdam (NL 32745) and the boards of directors of the participating local hospitals (Albert Schweitzer Hospital Dordrecht, St. Franciscus Gasthuis Rotterdam, Admiraal de Ruyter Hospital Goes and Amphia Hospital Breda) gave permission to execute the study locally. The study protocol and the amendments of the trial were registered in the International Standard Randomised Controlled Trials Number (ISRCTN) registry with protocol/serial number NL32745.078.10.

Study Design

This study was originally designed as a randomized, controlled multi-center trial with 3 treatment groups: PCN, ACD, and PT. It turned out that almost all of the eligible patients refused to participate in the PT group because they had previously been unsuccessfully treated with PT. They preferred to be treated with PCN or ACD, which resulted in a very slow inclusion rate. Therefore, we withdrew the PT-arm of the trial. This adjustment was approved by the MREC of the Erasmus University Medical Center Rotterdam and recorded in the ISRCTN-registry.

Patients

Eventually, patients were randomly assigned to one of 2 groups: PCN or ACD. Patients were included if they reported complaints of radicular pain of the lower cervical spine (C4 – C7) as a result of a single-level contained soft-disc hernia with or without neck pain and without improvement after at least 8 weeks of CT, such as anti-inflammatory medications, immobilization, PT, and epidural steroid injections. In addition, the intensity of their radicular arm pain had to be at least 50 millimetres (mm) on a visual analog scale (VAS) (0 = no pain and 100 = the worst pain imaginable). Excluded were patients with previous spinal surgery in the cervical region, an extruded disc fragment, a bony spur, a calcified disc, or severe degenerative disc disease with more than 50 percent loss of disc height. All patients were diagnosed by a neurologist based on clinical history, physical examination, and magnetic resonance imaging (MRI). They were also examined using needle electromyography to assess nerve root function and to rule out other neurological causes, such as ulnar or median entrapment neuropathies or peripheral neuropathy. Patients were recruited by the neurosurgeons of the Erasmus University Medical Center Rotterdam and the participating centers. Eligible patients were referred to an experienced staff neurosurgeon (B.H.) of the Erasmus University Medical Center Rotterdam or the St. Franciscus Gasthuis Rotterdam, who screened and included the patients. All patients gave written informed consent before enrollment into the trial. The results are reported in accordance with the updated guidelines of the Consolidated Standards of Reporting Trials (CONSORT) statement.[27]

Interventions

Both of the interventions performed in this study have been described earlier by our project team in 2 separate papers.[27,30] In these papers, the pre- and post-operative management is described as well as the surgical technique of PCN and ACD, accompanied by a video. Figure 1 illustrates the PCN technique.

Outcomes

The primary outcome measure was arm pain intensity measured with the VAS.[31] The VAS was measured on a horizontal 100 mm scale varying from 0 mm (no pain) to 100 mm (most intensive pain). The VAS has an adequate reliability and excellent validity in patients with chronic pain.[32,33] Secondary outcome measures were arm pain intensity during heavy effort measured with the VAS (such as squeezing, wringing, or typing)[31], neck pain intensity measured with the VAS[31], and satisfaction and improvement after the treatment measured with the Global Perceived Effect questionnaire (GPE).[34] GPE measures patient satisfaction and improvement after a treatment using a 7-point Likert scale.[34,35] Patient satisfaction was measured by answering the question: How satisfied are you with your treatment: 1 = very much satisfied to 7 = not at all satisfied. Improvement was measured by answering the question: Since the start of treatment, my current overall status is: 1 = very much improved to 7 = very much worse.[35] The GPE is regarded as valid and reliable.[36] In addition, disability due to neck pain was measured using the Neck Disability Index (NDI).[37] The NDI is the most often used outcome measure for self-reported disability in patients with neck pain.[37] The NDI is a 10-item questionnaire that measures pain intensity, daily work-related activities, and nonwork related activities.[38] The maximum score is 50. Scores of < 4 indicate no disability, 5 to 14 indicate mild disability, 15 to 24 moderate disability, 25 to 34 severe disability, and scores above 35 indicate complete perceived disability. This 50-point score was converted to a 100-point scale, where lower scores indicate less disability.[38] The NDI is reliable and valid for patients with cervical pathology.[36,37,39] Generic health status was measured as well, using the 36 Item Short Form Generated Health Survey (SF-36).[40] The SF-36 consists of 36 items on physical and social status of the patient divided into 8 subscales: 1-physical functioning, 2-role limitation due to physical health problems, 3-bodily pain, 4-general health perceptions, 5-vitality, 6-social functioning, 7-role limitations due to emotional problems, and 8-general mental health. The items were scored on a scale of 0 = worst health to 100 = ideal health. A higher score means a better self-reported health.[40] The SF-36 has a good reliability and validity.[33] We also recorded the number, nature, and severity of complications of the interventions. All parameters were measured at baseline (T0), 3 months after intervention (T2), and one year after intervention (T3). One week after the intervention (T1) an intermediate assessment of arm pain, arm pain during heavy effort, and neck pain, was performed using the VAS and satisfaction and improvement were measured with the GPE. The assessments were performed at the Research Unit of the Center for Pain Medicine of the Erasmus University Medical Center Rotterdam.

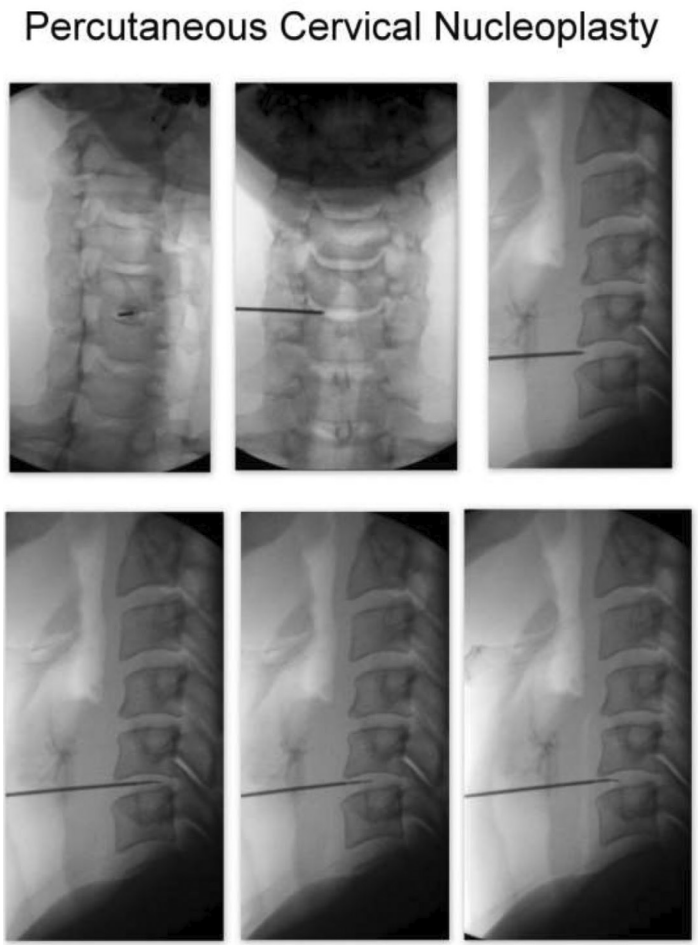

Figure 1: Technique of percutaneous cervical nucleoplasty.

Sample Size

As no results of previous studies were available, we chose a relatively small, but clinically relevant size within/between interaction effect with a minimum of (f (V)) of 0.35 on the pain intensity of the arm to be detectable. The power of the study (1 - β) was chosen to be 0.8 and the level of significance (α) to be 0.05. The required a priori total sample size computed by this method was 94.

Randomization

After providing written informed consent, the patients were randomized according to a computergenerated non-stratified block randomization program (www. randomization. com). An independent observer, who was not involved in the patients' outcome assessments, provided the trial coordinator with sealed envelopes containing the

randomization assignments. Envelopes were labelled according to the identification number of the study patients. For eligible patients, envelopes were opened in ascending order by the trial coordinator to determine the group allocation. Blinding due to the nature of the interventions, it was not possible to blind the interventionists and the patients. The data were analysed blindly.

Statistical Methods

Descriptive statistics were used to determine the frequencies of the demographic variables and to describe measures of central tendency and dispersion dependent on the shape of their distribution. The Kolmogorov-Smirnov test was used to analyze whether or not parameters were normally distributed. The linear mixed-model (LMM) to analyze repeated-measurement using the compound symmetry covariance structure was used, while group (PCN and ACD), time (moments of measurement), and the interaction between Group and Time (Group x Time) were entered as independent variables. Dependent variables were the primary and secondary outcome parameters. The LMM analysis is robust to handle missing data. An intention-to-treat (ITT) analysis with last observation carried forward and a per protocol (PP) analyses were performed, in which we compared the outcomes on T2 with those on T0 and T3 to T0. All analyses were performed using IBM SPSS Statistics for Windows, version 24 (IBM Corp, Armonk, New York, USA). For all statistics the alpha was set at the traditional 0.05 level.

Results

Sixty-seven eligible patients were screened for participation in this trial. Nineteen of them declined to participate, of whom 9 patients preferred a minimally invasive treatment with PCN and 8 patients preferred surgery. Two patients had less complaints and a wait and see policy was advised. Finally, 48 patients met the inclusion criteria and participated in this RCT. In Figure 2, the flowchart according to the Consolidated Standards of Reporting Trials is reported. The intended number of 94 patients was not achieved due to a low inclusion rate. It was estimated that the study would be finished after 2.5 years, but after one year we only enrolled 8 patients. After the adjustment of our protocol, we also expanded the trial with 3 centers to improve the inclusion rate. Despite this expansion the inclusion rate remained low and we decided to stop the trial. The last evaluation of the last included patient ended on March 2018. Forty-eight patients were randomly allocated to PCN (n = 24) and ACD (n = 24). No significant differences in baseline characteristics of the patients between the treatment groups were found (Table 1). The results of the descriptive statistics of the primary and secondary outcomes over time for both groups are presented in Table 2.

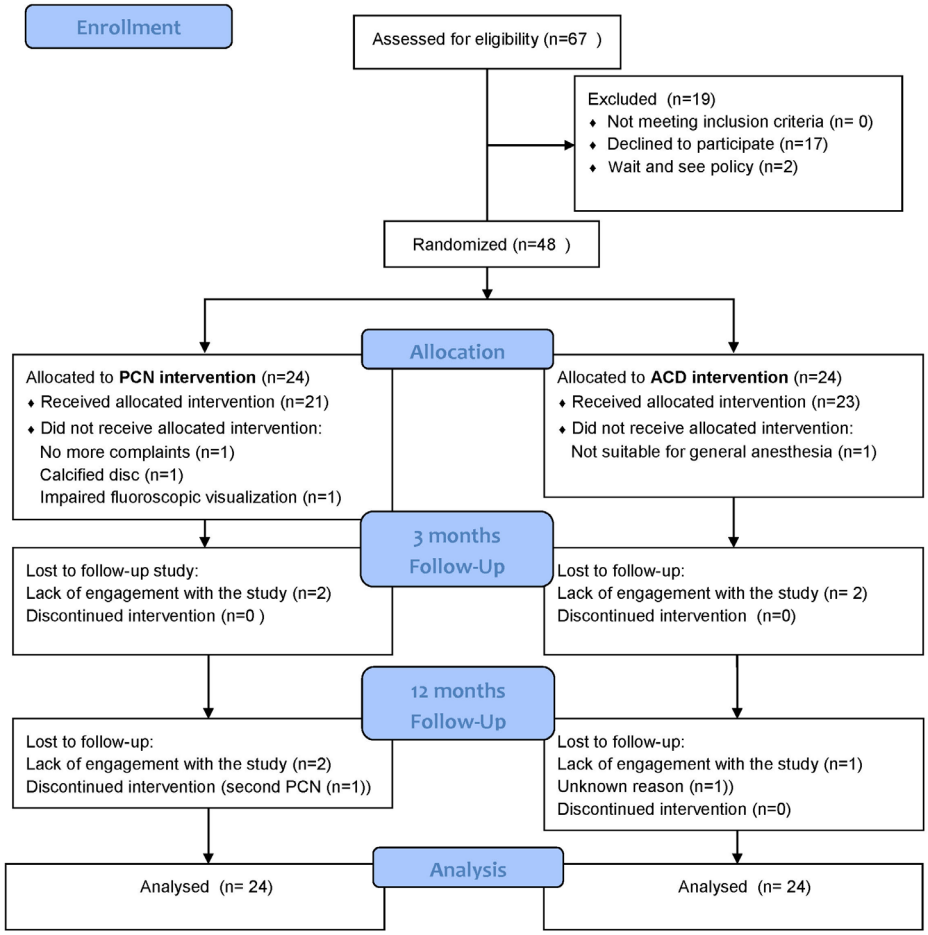

Figure 2: The flowchart according to the Consolidated Standards of Reporting Trials.

Item	PCN group	ACD group	P-value
Age (SD)	47 (9.24)	50 (9.24)	.122 †
Gender *n* (%)			.085 ɛ
Male	10 *(41.7)*	11 *(45.8)*	
Female	14 *(58.3)*	13 *(54.2)*	
Level of CHNP *n* (%)			2.087 ɛ
C4-5		1 *(4.2)*	
C5-6	13 *(54.2)*	9 *(37.5)*	
C6-7	11 *(45.8)*	14 *(58.3)*	
Treatment location *n* (%)			.085 ɛ
Right	10 *(41.7)*	11 *(45.8)*	
Left	14 *(58.3)*	13 *(54.2)*	
Total duration of pain in months mean (SD)	18.17 *(23.9)*	22.8 *(30.9)*	.309 †

CHNP, cervical hernia nucleus pulposus; SD, standard deviation, †, t-test; ɛ, pearson-χ2 .

Table 1: Patient characteristics at Baseline According to Study Arm.

Outcomes	ITT analyses		PP analyses	
	PCN group	ACD group	PCN group	ACD group
VAS arm (mm)				
Baseline	53.1 (4.60) [43.8-62.4]	58.9 (4.61) [49.7-68.3]	53.2 (4.59) [43.9-62.4]	58.9 (4.61) [49.6-68.2]
1 week	38.4 (6.00) [26.3-50.5]	41.9 (6.13) [29.6-54.3]	38.6 (6.17) [26.1-51.0]	38.7 (6.43) [25.7-51.7]
3 months	35.7 (5.74) [24.1-47.2]	24.3 (5.75) [12.7-35.9]	34.1 (5.80) [22.5-45.8]	18.3 (4.61) [6.43-30.1]
12 months	31.0 (5.49) [19.9-42.1]	21.3 (5.61) [10.0-32.6]	34.2 (5.61) [22.9-45.6]	19.5 (0.62) [07.0-31.9]
VAS arm during activities (mm)				
Baseline	70.4 (4.14) [62.0-78.7]	72.4 (4.23) [63.8-80.9]	70.4 (4.14)[62.0-78.7]	72.4 (4.23) [63.8-80.8]
1 week	35.9 (6.07) [30.6-56.5]	48.1 (6.20) [35.6-60.6]	52.4 (6.30) [39.7-65.1]	45.4 (6.43) [32.5-58.4]
3 months	43.5 (6.43) [30.6-56.5]	40.7 (6.57) [27.5-53.9]	42.7(6.80) [28.9-56.3]	40.7 (6.83) [26.9-54.5]
12 months	43.6 (6.38) [30.7-56.4]	32.0 (6.51) [18.9-45.1]	44.9 (7.08) [30.6-59.2]	29.7 (7.09) [15.4-44.1]
VAS neck (mm)				
Baseline	60.1 (4.60) [50.8-69.4]	59.9 (4.92) [50.1-69.9]	60.1 (4.60) [50.8-69.4]	60.1 (4.93) [50.1-70.0]
1 week	46.7 (5.55) [35.5-57.9]	48.9 (6.16) [50.5-70.4]	45.2 (5.77) [33.5-56.8]	46.5 (6.51) [33.3-59.6]
3 months	37.1 (5.70) [26.3-49.3]	26.0 (5.96) [13.9-38.0]	35.6 (5.90) [23.7-47.5]	24.5 (5.95) [12.5-36.6]
12 months	35.0 (5.41) [24.1-45.9]	24.7 (5.53) [13.5-35.8]	35.3 (5.64) [23.9-46.7]	21.2 (5.65) [09.7-32.6]
GPE-Satisfaction▪				
1 week	2.95 (0.29) [2.37-3.55]	2.46 (0.29) [1.83-3.06]	2.95 (0.29) [2.37-3.55]	2.46 (0.29) [1.83-3.06]
3 months	2.60 (0.34) [1.92-3.28]	1.97 (0.35) [1.26-2.67]	2.60 (0.34) [1.93-3.28]	1.97 (0.35) [1.26-2.67]
12 months	3.00 (0.32) [2.36-3.64]	2.27 (0.32) [1.62-2.92]	2.21 (0.31) [1.58-2.84]	1.80 (0.30) [1.19-2.41]
GPE-Improvement				
1 week	2.91 (0.25) [2.42-3.41]	2.90 (0.25) [2.40-3.41]	2.91 (0.25) [2.42-3.41]	2.90 (0.25) [2.40-3.41]
3 months	2.87 (0.29) [2.29-3.45]	2.34 (0.29) [1.75-2.93]	2.87 (0.29) [2.28-3.45]	2.34 (0.29)[1.75-2.93]
12 months	3.00 (0.32) [2.36-3.64]	2.27 (0.32) [1.62-2.92]	2.89 (0.35) [2.18-3.61]	2.26 (0.34) [1.57-2.96]
NDI▪				
baseline	61.88 (2.83) [56.17-67.59]	67.70 (2.83) [61.99-73.41]	61.88 (2.83) [56.17-67.59]	67.70 (2.83) [61.99-73.41]
3 months	49.09 (4.31) [40.40-57.76]	49.79 (4.31) [41.12-58.48]	48.68 (04.28) [40.03-57.32]	48.92 (4.28) [40.28-57.56]
12 months	46.13 (4.36) [37.35-54,91]	46.35 (4.36) [37.57-55.13]	46.01 (4.59) [36.71-55.30]	44.52 (4.59) [35.22-3.81]

Outcomes	ITT analyses		PP analyses	
	PCN group	ACD group	PCN group	ACD group
SF-36 Physical functioning				
baseline	60,00 (3.70) [52.55-67.46]	55.44 (3.78) [47.82-63.05]	60.00 (3.70) [52.55-67.46]	55.44 (3.78) [47.82-63.05]
3 months	66.67 (4.70) [57.19-76.14]	66.96 (4.80) [57.28-76.63]	67.46 (4.73) [57.93-77.00]	67.46 (4.73) [57.93-77.00]
12 months	72.50 (5.05) [62.33-82.68]	70.65 (5.16) [60.26-81.05]	73.25 (5.37) [62.40-84.09]	73.09 (5.39) [62.20-83.98]
Social functioning				
baseline	58.85 (5.04) [48.69-69.01]	53.80 (5.04) [48.69-69.01]	58.85 (5.04) [48.69-69.01]	53.80 (5.04) [48.69-69.01]
3 months	66.67 (5.41) [55.77-77.56]	66.30 (5.53) [55.18-77.43]	67.64 (5.49) [56.58-78.71]	67.30 (5.53) [56.14-78.47]
12 months	68.75 (5.97) [56.74-80.76]	72.28 (6.09) [60.01-84.56]	69.08 (6.43) [56.11-82.06]	75.52 (6.45) [62.49-88.55]
Physical role limitations				
baseline	21.88 (4.68) [12.45-31.30]	8.69 (4.78) [-0.93-18.32]	21.88 (4.68) [12.45-31.30]	8.69 (4.78) [-0.93-18.32]
3 months	35.42 (8.78) [17.73-53.11]	34.78 (8.97) [16.71-52.85]	37.26 (9.20) [18.71-55.82]	36.09 (9.22) [17.48-54.70]
12 months	59.38 (9.42) [40.39-78.36]	52.17 (9.63) [32.79-71.56]	64.46 (9.76) [44.42-83.89]	59.38 (9.77) [39.62-79.14]
Emotional role limitations				
baseline	63.89 (8.83) [46.11-81.67]	73.91(9.02) [55.75-92.08]	63.89 (8.83) [46.11-81.67]	73.91 (9.02) [55.75-92.08]
3 months	73.61 (9.12) [55.24-91.99]	65.21 (9.32) [46.45-83.99]	77.04 (9.10) [58.68-95.39]	65.63 (9.16) [47.14-84.12]
12 months	75.00 (8.71) [57.45-92.55]	72.46 (8.90) [54.54-90.39]	64.16 (9.75) [44.42-83.89]	59.38 (9.77) [39.62-79.14]
Mental health				
baseline	68.00 (3.63) [60.68-75.32]	69.04 (3.71) [61.56-76.52]	68.00 (3.63) [60.68-75.32]	69.04 (3.71) [61.56-76.52]
3 months	72.83 (3.32) [66.16-79.51]	72.00 (3.39)[65.18-78.82]	73.58 (3.26) [67.01-80.15]	72.28 (3.31) [65.61-78.95]
12 months	73.33 (3.13) [67.03-79.64]	73.04 (3.19) [66.60-79.49]	73.52 (3.07) [67.32-79.72]	74.13 (3.11) [67.84-80.43]
Vitality				
baseline	46.46 (3.70) [38.99-53.92]	42.61 (3.78) [34.99-50.23]	46.46 (3.70) [38.99-53.92]	42.61 (3.78) [34.99-50.23]
3 months	60.42 (4.78) [50.79-70.05]	51.96 (4.88) [42.12-61.79]	61.83 (4.72) [52.32-71.34]	52.42 (4.78) [42.79-62.05]
12 months	62.71 (4.57) [53.52-71.90]	55.44 (4.66) [46.05-64.82]	64.15 (4.73) [54.61-73.69]	55.56 (4.76) [45.94-65.18]

Outcomes	ITT analyses		PP analyses	
	PCN group	ACD group	PCN group	ACD group
Pain				
baseline	38.18 (3.78) [30.57-45.79]	29.02 (3.86) [21.25-36.79]	38.18 (3.78) [30.57-45.79]	29.02 (3.86) [21.25-36.79]
3 months	52.64 (5.35) [41.86-63.42]	59.63 (5.47) [48.61-70.64]	54.29 (5.45) [43.30-65.28]	61.14 (5.47) [50.10-72.17]
12 months	63.61 (5.48) [52.58-74.63]	62.38 (5.59) [51.11-73.64]	65.22 (5.92) [53.23-77.19]	64.19 (5.92) [52.21-76.18]
General Health				
baseline	62.71 (4.29) [54.06-71.36]	55.65 (4.39) [46.82-64.49]	62.71 (4.29) [54.06-71.36]	55.65 (4.39) [46.82-64.49]
3 months	68.96 (4.51) [59.88-78.03]	55.22 (4.60) [45.95-64.49]	70.15 (4.52) [61.04-79.27]	55.41 (4.57) [46.21-64.62]
12 months	63.33 (4.65) [53.97-72.70]	65.21 (4.7 5) [55.65-74.79]	61.42 (4.91) [51.49-71.35]	66.66 (4.95) [56.65-76.68]

Data are presented as Mean (Standard Error) [95% Confidence Interval] of the linear mixed-model analyses.
▪ A lower score means better outcomes with regard to satisfaction and improvement (GPE) and less disability in daily activities due to neck pain (NDI).
▪▪ A higher score means a better health-related quality of life status (SF-36).
Table 2: The results of the descriptive statistics of the primary and secondary outcomes over time for both groups.

Outcomes

ITT Analyses: Baseline Compared to 3 Months

Regardless of the intervention made (i.e., all patients pooled together), it turned out that they improved significantly over time on the primary outcome arm pain and on the secondary outcomes arm pain during heavy effort, neck pain, NDI and the SF-36 items physical functioning, social functioning, physical role limitations, mental health, vitality, and pain. We did not find statistically significant group effects on any outcomes. A statistically significant interaction on the primary outcome arm pain ($F(1,44) = 4.131$; $P = 0.05$) and on the item pain of the secondary outcome of the SF-36 ($F(1,45) = 5.245$; $P = 0.03$) were found in favor of the ACD group. On the other secondary outcomes no statistically significant interactions were found. In Table 3, the results on these parameters are presented over time and by experimental group. Figure 3 illustrates the amount of arm pain between the groups in time.

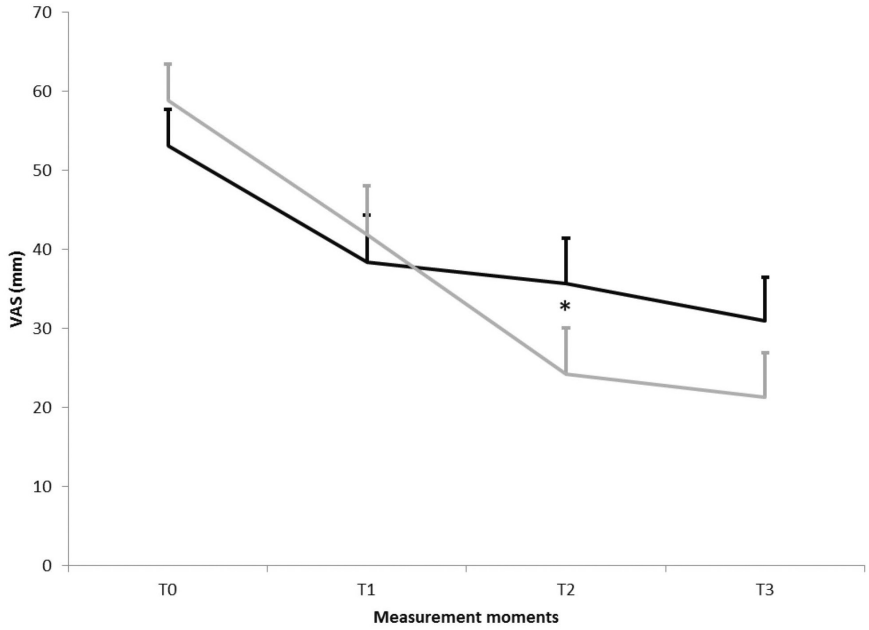

Figure 3: The intensity of arm pain between treatment groups at all measurement moments.
*P < 0.05; PCN, percutaneous cervical nucleoplasty group depicted as black; ACD, anterior cervical discectomy group depicted as grey.

ITT Analyses: Baseline Compared to 12 Months

Regardless of the intervention made, all pooled patients improved significantly over time on the primary outcome arm pain and on the secondary outcomes arm pain during heavy effort, neck pain, NDI and the SF-36 items physical functioning, physical role limitations, mental health, vitality and pain. We did not find a statistically significant

group effect on the primary and secondary outcomes and no statistically significant interactions on the primary and secondary outcomes (Table 3).

PP Analyses: Differences with Respect to the ITT Analysis

At 3 months, the results of the PP analyses was almost the same as the ITT analyses. An additional statistically significant effect was found on the time factor of the secondary outcome satisfaction of the GPE ($F(1,40) = 4.818$; $P = 0.03$) (Table 3). At 12 months, the results of the PP analyses was also almost the same as the ITT analyses, but an additional statistically significant interaction was found on the item of general health of the SF-36 ($F(1,39) = 4.290$; $P = 0.05$), which was in favor of the ACD group (Table 3).

Adverse Effects

Three patients in the ACD group experienced adverse effects that were directly related to the operation. Two of these patients had severe postoperative neck pain and were treated with a stiff neck collar. In both patients, the neck pain disappeared within 3 months. Another patient in the ACD treatment group experienced postoperative dysphonia and dysphagia, which fully resolved within 3 months. In one patient who was treated with ACD, the complaints continued after surgery. However, this event was not directly related to the operation, a new MRI was performed and showed that the disc herniation was treated successfully. In the PCN group, no adverse events occurred directly related to the procedure. Two patients could not be treated with PCN due to the fact that the pain-specialist was not able to insert the introducer cannula into the herniated disc; we have described these failed procedures earlier in the results. Eventually, both of these patients were sent to the neurosurgeon and were successfully treated with an ACD. Another patient in the PCN group developed a cervical disc herniation on the adjacent lower level (C4-5) 3 months after the intervention. A MRI was performed and showed new global bulgings of the discs C4-5 and C5-6. This patient was also successfully treated with an ACD at C5-6, but kept postoperative complaints of dysphagia. One patient in the PCN group, who was initially treated successfully, experienced CRP again 6 months after the treatment. A MRI showed a bulging disc at the same level as before. This patient preferred to be treated with PCN again and this was done successfully.

Outcomes	ITT analyses			PP analyses		
	Between Groups	Time	Interaction between group and time	Group	Time	Interaction group and time
	P Value	P Value	P Value	P Value	P Value	P Value
Visual analogue scale						
Arm pain						
3 months	$F_{(1,45)}$=0.204; p=0.65	$F_{(1,44)}$=38.154; p<0.001***	$F_{(1,44)}$=4.131; p=0.05*	$F_{(1,45)}$=0.615; p=0.44	$F_{(1,42)}$=44.348; p<0.001***	$F_{(1,40)}$=6.103; p=0.02*
12 months	$F_{(1,45)}$=0.920; p=0.76	$F_{(1,45)}$=41.246; p<0.001***	$F_{(1,45)}$=3.052; p=0.09	$F_{(1,44)}$=0.156; p=0.69	$F_{(1,40)}$=38.829; p<0.001***	$F_{(1,40)}$=6.103; p=0.09
Arm pain during activities						
3 months	$F_{(1,45)}$=0.005; p=0.95	$F_{(1,45)}$= 047.797; p<0.001***	$F_{(1,45)}$=0.324; p =0.57	$F_{(1,44)}$=0.000; p=0.99	$F_{(1,40)}$= 2.207; p<0.001***	$F_{(1,42)}$=0.195; p=0.66
12 months	$F_{(1,45)}$=0.623; p=0.43	$F_{(1,45)}$= 51.136; p<0.001***	$F_{(1,45)}$=2.085; p=0.16	$F_{(1,40)}$=1.048; p=0.31	$F_{(1,39)}$=44.466; p<0.001***	$F_{(1,39)}$=2.824; p=0.10
Neck pain						
3 months	$F_{(1,41)}$=0.858; p=0.36	$F_{(1,40)}$=51.402; p<0.001***	$F_{(1,40)}$=2.207; p=0.15	$F_{(1,41)}$=0.754; p=0.39	$F_{(1,36)}$=54.916; p<0.001***	$F_{(1,36)}$=1.834; p=0.18
12 months	$F_{(1,44)}$=0.685; p=0.41	$F_{(1,44)}$=43.347; p<0.001***	$F_{(1,44)}$=1.536; p=0.22	$F_{(1,42)}$=1.414; p=0.24	$F_{(1,40)}$=44.022; p<0.001***	$F_{(1,40)}$=2.423; p=0.13
Global perceived effect Satisfaction						
3 months	$F_{(1,43)}$=1.881; p=0.18	$F_{(1,43)}$=4.967; p=0.31	$F_{(1,43)}$=0.088; p=0.77	$F_{(1,43)}$=1.931; p=0.17	$F_{(1,40)}$=4.818; p=0.03*	$F_{(1,40)}$=0.126; p=0.73
12 months	$F_{(1,42)}$=2.038; p=0.16	$F_{(1,42)}$=6.997; p=0.18	$F_{(1,42)}$=0.029; p=0.87	$F_{(1,42)}$=2.038; p=0.16	$F_{(1,42)}$=6.097; p=0.02*	$F_{(1, 41)}$=0.029; p=0.87
Improvement						
3 months	$F_{(1,44)}$=0.630; p=0.43	$F_{(1,44)}$=1.756; p=0.19	$F_{(1,44)}$=1.249; p=0.27	$F_{(1,44)}$=0.744; p=0.39	$F_{(1,42)}$=1.935; p=0.17	$F_{(1,42)}$=1.380; p=0.25
12 months	$F_{(1,36)}$=1.269; p=0.27	$F_{(1,36)}$=1.269; p=0.28	$F_{(1,36)}$=1.143; P=0.29	$F_{(1,36)}$=1.056; p=0.31	$F_{(1,35)}$=1.269; p=0.27	$F_{(1,35)}$=1.143; p=0.29
Neck disability index						
3 months	$F_{(1,44)}$=0.506; p=0.48	$F_{(1,44)}$=43.006; p<0.001***	$F_{(1,44)}$=1.191; p=0.28	$F_{(1,44)}$=0.478; p=0.44	$F_{(1,42)}$=45.241; p<0.001***	$F_{(1,42)}$=1.267; p=0.27
12 months	$F_{(1,44)}$=0.494; p=0.49	$F_{(1,44)}$=40.154; p<0.001***	$F_{(1,44)}$=0.916; p=0.34	$F_{(1,40)}$=0.247; p=0.62	$F_{(1,40)}$=37.405; p<.0001***	$F_{(1,38)}$=1.310; p=0.26
Short Form-36 Physical functioning						
3 months	$F_{(1,45)}$=0.148; p=0.70	$F_{(1,45)}$=14.748; p<0.001***	$F_{(1,45)}$=1.051; p=0.31	$F_{(1,45)}$=0.159; p=0.69	$F_{(1,40)}$=15.406; p<0.001***	$F_{(1,42)}$=0.896; p=0.35
12 months	$F_{(1,45)}$=0.340; p=0.56	$F_{(1,45)}$=19.452; p<0.001***	$F_{(1,45)}$=0.187; P=0.67	$F_{(1,43)}$=0.185; p=0.67	$F_{(1,39)}$=18.655; p <0.001***	$F_{(1,38)}$=0.379; p=0.54
Social functioning						
3 months	$F_{(1,45)}$=0.159; p=0.69	$F_{(1,45)}$=10.603; p<0.002**	$F_{(1,45)}$=0.565; p=0.46	$F_{(1,43)}$=0.159; p=0.69	$F_{(1,45)}$=11.475; p<0.002**	$F_{(1,43)}$=0.513; p=0.48*
12 months	$F_{(1,45)}$=0.045; p=0.83	$F_{(1,45)}$=0.158; p=0.22	$F_{(1,45)}$=0.369; p=0.55	$F_{(1,46)}$=0.010; p=0.92	$F_{(1,40)}$=13.195; p<0.001***	$F_{(1,39)}$=1.705; p=0.19

Outcomes	ITT analyses			PP analyses		
	Between Groups	Time	Interaction between group and time	Group	Time	Interaction group and time
	P Value	P Value	P Value	P Value	P Value	P Value
Physical role limitations						
3 months	$F_{(1,45)}$=0.710; p=0.40	$F_{(1,45)}$= 11.556; p<0.001***	$F_{(1,45)}$=1.158; p=0.29	$F_{(1,44)}$=0.745; p=0.39	$F_{(1,42)}$=11.989; p<0.001***	$F_{(1,43)}$=0.944; p=0.34
12 months	$F_{(1,45)}$= 1.463; p=0.23	$F_{(1,45)}$=38.931; p<0.001***	$F_{(1,45)}$=0.212; p=0.65	$F_{(1,43)}$=1.160; p=0.29	$F_{(1,39)}$=44.900; p<0.001***	$F_{(1,38)}$=0.366; p=0.55
Emotional role limitations						
3 months	$F_{(1,45)}$=0.005; p=0.94	$F_{(1,45)}$=0.08; p= 0.93	$F_{(1,45)}$=2.628; p=0.11	$F_{(1,44)}$=0.004; p=0.95	$F_{(1,44)}$=0.161; p=0.69	$F_{(1,42)}$=3.124; p=0.08
12 months	$F_{(1,45)}$=0.132; p=0.72	$F_{(1,45)}$=0.461; p=0.50	$F_{(1,45)}$=0.779; p=0.38	$F_{(1,42)}$=0.392; p=0.53	$F_{(1,40)}$=1.973; p=0.17	$F_{(1,40)}$=0.269; p=0.61
Mental health						
3 months	$F_{(1,45)}$=0.000; p=0.98	$F_{(1,45)}$= 8.776; p=0.005**	$F_{(1,45)}$=0.509; p=0.48	$F_{(1,45)}$=0.001; p=0.98	$F_{(1,43)}$=10.122; p<0.003**	$F_{(1,42)}$=0.717; p=0.40
12 months	$F_{(1,45)}$=0.007; p=0.94	$F_{(1,45)}$=10.451; p=0.002**	$F_{(1,45)}$=0.213; p=0.65	$F_{(1,44)}$=0.033; p=0.86	$F_{(1,39)}$=11.627; p<0.002**	$F_{(1,38)}$=0.019; p=0.89
Vitality						
3 months	$F_{(1,45)}$=1.166; p=0.29	$F_{(1,45)}$=27.833; p<0.001***	$F_{(1,45)}$=1.089; p=0.30	$F_{(1,45)}$=1.405; p=0.24	$F_{(1,42)}$=29.922; p <0.001***	$F_{(1,42)}$=1.456; p=0.23
12 months	$F_{(1,45)}$=1.057; p=0.31	$F_{(1,45)}$=35.034; p<0.001***	$F_{(1,45)}$=0.486; p=0.49	$F_{(1,44)}$=1.340; p=0.25	$F_{(1,38)}$=30.724; p <0.001	$F_{(1,38)}$=0.736; p=0.39
Pain						
3 months	$F_{(1,45)}$=0.038; p=0.85	$F_{(1,45)}$=40.809; p<0.001***	$F_{(1,45)}$=5.245; p=0.03*	$F_{(1,45)}$=0.043; p=0.84	$F_{(1,43)}$=43.650; p <0.001	$F_{(1,42)}$=4.809; p=0.03*
12 months	$F_{(1,45)}$=1.003; p=0.32	$F_{(1,45)}$=47.222; p<0.001***	$F_{(1,45)}$=0.861; p=0.36	$F_{(1,43)}$=0.946; p=0.34	$F_{(1,42)}$=43.602; p <0.001	$F_{(1,41)}$=0.747; p=0.39
General Health						
3 months	$F_{(1,45)}$=3.205; p=0.08	$F_{(1,45)}$=1.446; p=0.24	$F_{(1,45)}$=1.911; p=0.17	$F_{(1,45)}$=3.612; p= 0.64	$F_{(1,42)}$=1.964; p=0.17	$F_{(1,42)}$=2.233; p=0.14
12 months	$F_{(1,45)}$=0.203; p=0.66	$F_{(1,45)}$=3.265; p=0.08	$F_{(1,45)}$=2.513; p=0.12	$F_{(1,44)}$=0.024; p=0.88	$F_{(1,39)}$=2.685; p=0.11	$F_{(1,39)}$=4.290; p=0.05*

Statistical outcome of the overall LMM with fixed effects was set at a level of significance of 0.05, *, p <0.05; **,p <0.01; ***, p <0.001

Table 3: results from intention to treat (ITT) and per-protocol (PP) analyses over time by experimental group.

Discussion

In this trial, the effects of PCN were compared to ACD in 48 patients with CRP caused by a single level contained soft-disc hernia. Three months after the intervention the ACD patients reported statistically significant less arm pain than the PCN patients. At 12 months, only a trend was found for more improvement on arm pain in the ACD group. Furthermore, no statistically significant interactions were found on the secondary outcomes. There are only a few studies comparing PCN to surgery. The first study is a recently performed RCT that compared the effects of PCN to posterior decompression in patients suffering from single level disc herniation with an indication for surgery (n = 35).[41] In this trial, no significant differences were found between the groups on radicular arm pain and neck pain 3 and 6 months after the intervention.[41] A second study was a retrospective study that compared PCN (n = 81) to ACD (n = 95) in patients with a contained disc herniation.[25] At about 29 months, they did not find a statistically significant difference in pain reduction between PCN and ACD. The findings of the first study[41] is in contrast with the findings of our study at 3 months. However, at the longer-term (i.e., 6 months and longer), the results of these studies [25,41] might be in confirmation with our trial results. The success rate of PCN depends on strict patient selection.[21] Two recent retrospective studies examined the ideal selection criteria of a successful PCN[21,42] and found that the following selection criteria are predictive for a positive outcome of PCN: MRI confirmed one-level contained herniated discs, minimally degenerated discs, short mean pain duration of respectively 6, 8[42], and 16 months[21], absence of central canal stenosis, and unilateral radicular pain rather than bilateral radicular or axial neck pain only.[21,42]

The inclusion criteria of our patients matched with these criteria with the exception of a short pain duration. The mean pain duration of our PCN group was at baseline 18.17 months, which fell within the range of the mean pain duration of patients with a negative outcome of the PCN procedure, respectively 10.85[42] to 37 months.[21] This may have had a negative impact on the outcomes of our PCN group. At 3 months, our ACD patients showed statistically significant more reduction in arm pain intensity compared to the PCN patients, namely an average of 17.2 mm on a VAS scale of 100 mm. It is debatable whether or not this difference is of clinical relevance. To further investigate clinical relevance of this difference, we divided the patients into those who showed an improvement in arm pain of ≥ 30.0 mm on the VAS and those who did not. A mean reduction in VAS of 30 mm represents a clinically important difference in pain severity that corresponds to patients' perception of adequate pain control.[43] We found that the proportion of patients who met this criterion did not differ between the experimental groups (P = 0.11, Fisher's Exact Test 2-sided). Considering this, the absence of a difference in arm pain relief between the groups after one year, the smaller number of complications within the PCN group, and the minimally invasive technique

of PCN, we argue that PCN can be a good alternative to ACD, certainly from a longer-term perspective.

Limitations

This study had several limitations. Firstly, the inclusion by the participating hospitals was limited, because several patients preferred to be treated in their local hospital. Therefore, most patients who participated in this trial came from the Erasmus University Medical Center Rotterdam and the St. Franciscus Gasthuis Rotterdam. This could have limited the external validity of our trial. Secondly, the trial was ended before reaching the required sample size. This was due to the limited number of eligible patients, resulting probably in a heightened type II error and consequently a limitation of the internal validity of our study. Despite that, we did find a significant difference between the groups on reduction in arm pain intensity at 3 months. At 12 months, we did not find any significant interaction on any outcomes anymore, which could be due to the fact that our trial was underpowered. A third limitation was that at baseline, 13 patients scored less than 50 mm on VAS arm pain (7 patients had a between 49-40 mm, 3 patients between 30-20 mm, and another 3 had a VAS arm of less than 0.30 mm). While all these patients scored a VAS on arm pain intensity of 50 mm or higher, respectively 1 to 2 weeks before baseline, at the inclusion by the neurosurgeon. These patients all indicated that their arm pain was variable in time and during heavy effort, which effected their daily life and hence preferred surgical intervention. We performed post hoc ITT analyses without these 13 patients, and no longer found a significant interaction between the groups over time on the primary or secondary outcomes. It should be noted that this outcome of the post hoc ITT analysis does not mean that both interventions are more effective in patients with a higher VAS score (> 70 mm). Further studies have to be performed. A fourth limitation was that we had to withdraw our PT group. It would have been of importance to get more insight in the effect of PT to PCN and ACD, as these interventions never have been compared in a RCT before. Finally, due to the nature of the interventions, patients and interventionists could not be blinded for the treatment, which could have increased the risk of performance bias.

Conclusions

Although the ACD group reported better statistical significance reduction on arm pain than the PCN group 3 months after the interventions, the clinical relevancy of this difference in treatment effect can be debated. We conclude that in the long- term PCN can be a good alternative for ACD. Future research should be focussed on evaluating the optimal time frame for a PCN. Larger trials should be performed to compare the effects of CT, surgery, and PCN.

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Author Contributions

All authors equally contributed to the design, conduct, analyses, writing of the manuscript, and approved the final version of the article.

REFERENCES

1. Wullems JA, Halim W, van der Weegen W. Current evidence of percutaneous nucleoplasty for the cervical herniated disk: A systematic review. Pain Pract 2014; 14:559-569.
2. Kuijper B, Tans JTJ, Beelen A, Nollet F, de Visser M. Cervical collar or physiotherapy versus wait and see policy for recent onset cervical radiculopathy: Randomised trial. BMJ 2009; 339:b3883.
3. Radhakrishnan K, Litchy WJ, O'Fallon WM, Kurland LT. Epidemiology of cervical radiculopathy. A populationbased study from Rochester, Minnesota, 1976 through 1990. Brain 1994; 117 (Pt 2):325-335. 4. Carette S, Fehlings MG. Clinical practice. Cervical radiculopathy. N Engl J Med 2005; 353:392-399.
5. Wong JJ, Cote P, Quesnele JJ, Stern PJ, Mior SA. The course and prognostic factors of symptomatic cervical disc herniation with radiculopathy: A systematic review of the literature. Spine J 2014; 14:1781-1789.
6. Caridi JM, Pumberger M, Hughes AP. Cervical radiculopathy: A review. Hss J 2011; 7:265-272. 7. Woods BI, Hilibrand AS. Cervical radiculopathy: Epidemiology, etiology, diagnosis, and treatment. J Spinal Disord Tech 2015; 28:E251-E259.
8. de Rooij JD, Gadjradj PS, Huygen FJ, Luijsterburg PAJ, Harhangi BS. Management of symptomatic cervical disk herniation: A survey among Dutch neurosurgeons. Spine (Phila Pa 1976) 2017; 42:311-317. 9. Jacobs W, Willems PC, Kruyt M, et al. Systematic review of anterior interbody fusion techniques for single- and double-level cervical degenerative disc disease. Spine (Phila Pa 1976) 2011; 36:E950-E960. 10. Vleggeert-Lankamp CLA, Janssen TMH, van Zwet E, et al. The NECK trial: Effectiveness of anterior cervical discectomy with or without interbody fusion and arthroplasty in the treatment of cervical disc herniation; A doubleblinded randomised controlled trial. Spine J 2019; 19:965-975.
11. Botelho RV, Dos Santos Buscariolli Y, de Barros Vasconcelos Fernandes Serra MV, Nogueira Pires Bellini M, Marques Bernardo W. The choice of the best surgery after single level anterior cervical spine discectomy: A systematic review. Open Orthop J 2012; 6:121-128.
12. Donk RD, Verbeek ALM, Verhagen WIM, Groenewoud H, Hosman AJF, Bartels RHM. What's the best surgical treatment for patients with cervical radiculopathy due to single-level degenerative disease? A randomized controlled trial. PLoS One 2017; 12:e0183603.
13. Yang X, Janssen T, Arts MP, Peul WC, Vleggeert-Lankamp CLA . Radiological follow-up after implanting cervical disc prosthesis in anterior discectomy: A systematic review. Spine J 2018; 18:1678-1693.
14. Nabhan A, Pape D, Pitzen T, et al. Radiographic analysis of fusion progression following one-level cervical fusion with or without plate fixation. Zentralbl Neurochir 2007; 68:133-138.
15. Nanda A, Sharma M, Sonig A, Ambekar S, Bollam P. Surgical complications of anterior cervical diskectomy and fusion for cervical degenerative disk disease: A single surgeon's experience of 1,576 patients. World Neurosurg 2014; 82:1380-1387.
16. Bovonratwet P, Fu MC, Tyagi V, et al. Incidence, risk factors, and clinical implications of postoperative hematoma requiring reoperation following anterior cervical discectomy and fusion. Spine (Phila Pa 1976) 2019; 44:543-549.
17. Koreckij TD, Gandhi SD, Park DK. Cervical disk arthroplasty. J Am Acad Orthop Surg 2019; 27:e96-e104.
18. Gerges FJ, Lipsitz SR, Nedeljkovic SS. A systematic review on the effectiveness of the Nucleoplasty procedure for discogenic pain. Pain Physician 2010; 13:117-132.
19. Chen YC, Lee SH, Saenz Y, Lehman NL. Histologic findings of disc, end plate and neural elements after coblation of nucleus pulposus: An experimental nucleoplasty study. Spine J 2003; 3:466-470
20. Chen YC, Lee SH, Chen D. Intradiscal pressure study of percutaneous disc decompression with nucleoplasty in human cadavers. Spine (Phila Pa 1976) 2003;28(7):661-5.
21. Halim W, Wullems JA, Lim T, et al. The long-term efficacy and safety of percutaneous cervical nucleoplasty in patients with a contained herniated disk. Pain Pract 2013; 13:364-371.

22. Birnbaum K. Percutaneous cervical disc decompression. Surg Radiol Anat 2009; 31:379-387.
23. Cesaroni A, Nardi PV. Plasma disc decompression for contained cervical disc herniation: A randomized, controlled trial. Eur Spine J 2010; 19:477-486.
24. Bonaldi G, Baruzzi F, Facchinetti A, Fachinetti P, Lunghi S. Plasma radio-frequency-based diskectomy for treatment of cervical herniated nucleus pulposus: Feasibility, safety, and preliminary clinical results. AJNR Am J Neuroradiol 2006; 27:2104-2111.
25. Yan D, Li J, Zhu H, Zhang Z, Duan L. Percutaneous cervical nucleoplasty and percutaneous cervical discectomy treatments of the contained cervical disc herniation. Arch Orthop Trauma Surg 2010; 130:1371-1376.
26. Azzazi A, Elhawary Y. Cervical nucleoplasty using coblation technology; Clinical outcome. Neurosurg Q 2010; 20:146-150.
27. de Rooij JD, Gadjradj PS, Soria van Hoeve JS, Huygen FJ, Aukes HA, Harhangi BS. Percutaneous nucleoplasty for the treatment of a contained cervical disk herniation. Clin Spine Surg 2017; 30:389-391. 28. Li S, Chen R, Chen Y, et al. Therapeutic effects and safety of percutaneous disc decompression with coblation nucleoplasty in cervical vertigo: A retrospective outcome study with 74 consecutive patients and minimum 1-year follow-up. Pain Physician 2019; 22:E205-E214.
29. Moher D, Hopewell S, Schulz KF, et al. CONSORT 2010 explanation and elaboration: Updated guidelines for reporting parallel group randomised trials. Int J Surg 2012; 10:28-55.
30. de Rooij JD, Gadjradj PS, Soria van Hoeve JS, Harhangi BS. Anterior cervical discectomy without fusion for a symptomatic cervical disk herniation. Acta Neurochir (Wien) 2017; 159:1283-1287.
31. Carlsson AM. Assessment of chronic pain. I. Aspects of the reliability and validity of the visual analogue scale. Pain 1983; 16:87-101.
32. Jensen MP, McFarland CA. Increasing the reliability and validity of pain intensity measurement in chronic pain patients. Pain 1993; 55:195-203.
33. McCarthy MJ, Grevitt MP, Silcocks P, Hobbs G. The reliability of the Vernon and Mior neck disability index, and its validity compared with the short form36 health survey questionnaire. Eur Spine J 2007; 16:2111-2117.
34. Likert R. A technique for the measurement of attitudes. Archives of Psychology 1932; 22 140:55.
35. Farrar JT, Young JP Jr, LaMoreaux L, Werth JL, Poole RM. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. Pain 2001; 94:149-158.
36. Kamper SJ, Ostelo RW, Knol DL, Maher CG, de Vet HCW, Hancock MJ. Global perceived effect scales provided reliable assessments of health transition in people with musculoskeletal disorders, but ratings are strongly influenced by current status. J Clin Epidemiol 2010; 63:760-766.e1.
37. Young IA, Cleland JA, Michener LA, Brown C . Reliability, construct validity, and responsiveness of the neck disability index, patient-specific functional scale, and numeric pain rating scale in patients with cervical radiculopathy. Am J Phys Med Rehabil 2010; 89:831-839.
38. Vernon H, Mior S. The Neck Disability Index: A study of reliability and validity. J Manipulative Physiol Ther 1991; 14:409-415.
39. Vos CJ, Verhagen AP, Koes BW. Reliability and responsiveness of the Dutch version of the Neck Disability Index in patients with acute neck pain in general practice. Eur Spine J 2006; 15:1729-1736.
40. Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF36). I. Conceptual framework and item selection. Med Care 1992; 30:473-483.
41. Abrishamkar S, Salimi S, Pirmoradi H. Comparison the postoperation results of discectomy with nucleoplasty in single cervical disc herniation. Adv Biomed Res 2018; 7:29.
42. Kim MK, Sim SE, Kim YC, et al. Predictive factors of successful percutaneous cervical nucleoplasty for the treatment of pain with cervical herniated disk. World Neurosurg 2018; 114:e654-e662.
43. Lee JS, Hobden E, Stiell IG, Wells GA . Clinically important change in the visual analog scale after adequate pain control. Acad Emerg Med 2003; 10:1128-1130.

Chapter eight

LONG-TERM CLINICAL RESULTS OF PERCUTANEOUS CERVICAL NUCLEOPLASTY FOR CERVICAL RADICULAR PAIN: A RETROSPECTIVE COHORT STUDY

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Abstract

Purpose

Percutaneous cervical nucleoplasty (PCN) is a minimally invasive treatment for cervical radicular pain due to a disc herniation. Preliminary results show equivalent patient-reported outcomes of PCN as compared to conventional anterior cervical discectomy. However, there is a paucity of long-term outcome data. Therefore, the primary objective of this study is to investigate the long-term clinical results of PCN.

Patients and Methods

A retrospective analysis was conducted on patients who underwent PCN at a secondary referral center between 2010 and 2014. Before surgery and five days after surgery, numeric rating scales (NRS) for arm pain and neck pain and data on complications were collected. To determine long-term follow-up outcomes, patients were sent a questionnaire booklet containing the Core Outcome Measures Index-Neck (COMI-Neck), NRS for arm pain and neck pain, Likert-scales on patient satisfaction and questions regarding the incidence of reoperations and complications.

Results

The baseline characteristics were collected for 158 patients. At a median follow-up of 41.5 months (interquartile range (IQR) 27.0 to 57.5), data were available for 118 patients (74.7%). At short-term follow-up, patients that underwent PCN had a mean decrease of 3.0 on the NRS for arm pain (95% CI 2.5 to 3.6) compared to baseline, while at long-term follow-up, a mean decrease of 2.8 (95% CI 1.0 to 3.6) was observed. At the long-term follow-up, 67.8% of the patients were fully recovered from all symptoms and 93.3% remained satisfied with the PCN treatment results. The reoperation rate for recurrent disc herniation was 21.4% at long-term follow-up.

Conclusion

PCN appears to be a safe and effective treatment at short-term and long-term follow-up of a specific selection of cervical herniated discs, with an acceptable long-term reoperation rate. These study results suggest a potential role of PCN as a less invasive treatment option for cervical radicular pain due to a soft disc herniation, before anterior cervical discectomy should be considered.

Introduction

Symptomatic herniated cervical discs cause neck and radiating arm pain as a result of compression of the cervical spinal nerve.[1] Cervical radicular pain has a high impact on the patient's quality of life[2] and the natural course appears to be favourable.[3] At six months, 42% of the patients who received conservative treatment recovered from neck pain and 59% of the patients reported no or only slight arm pain.[3] At 12 months, almost 50% of the patients recovered from both neck and arm pain.[3] When the severe pain persists and does not improve with conservative care, surgery may be considered. In the 1940s and the 1950s the posterior cervical foraminotomy and the anterior cervical discectomy with fusion (ACDF) techniques were developed to treat cervical disc herniation.[4] ACDF is nowadays the preferred technique to treat symptomatic cervical disc herniation,[5,6] however two recent trials revealed that anterior cervical discectomy (ACD) seems to achieve similar results as ACDF.[6,7] Although ACDF is a safe and effective procedure to treat cervical radicular pain, rare but potentially dangerous risks can occur during or after surgery such as oesophageal injury, postoperative hematoma and mortality.[8–10] To reduce these risks of surgery, new minimally invasive techniques and instruments for spine surgery have been developed in the last two decades.[11] Compared to conventional anterior open methods, these minimally invasive techniques in spine surgery have several advantages such as smaller incisions, less soft tissue injury, shorter hospital stay, less blood loss and faster return to normal daily activities.[11–13] One of the minimally invasive techniques that could potentially answer this need is percutaneous cervical nucleoplasty (PCN). PCN uses coblation technology for ablating and coagulating the soft tissue of the herniated disc.[14,15] Strict patient selection, however, is important for a successful outcome after PCN.[16,17] In particular, patients with minimally degenerated discs, the absence of central canal stenosis, and unilateral radicular pain will benefit most from this procedure.[16,17] PCN is an effective and safe technique in the reduction of pain in patients with cervical radicular pain due to a disc herniation.[16,18–21] The efficacy of PCN has been demonstrated from two months up to two years of follow-up.[16,18–21] Long-term evidence on the effectiveness and safety of PCN, however, is lacking. Therefore, the primary objective of this retrospective cohort study was to evaluate the clinical long-term effects of PCN on arm pain in patients with cervical radicular pain due to a disc herniation. The secondary aim was to evaluate long-term function, symptom-specific wellbeing, quality of life, disability and patient satisfaction in patients with cervical radicular pain due to a disc herniation.

Methods

Patient Population and Indication

Consecutive patients who received PCN for cervical radicular pain due to a contained soft-disc herniation between 2010 and 2014 were included in this single-center retrospective cohort study at Albert Schweitzer Hospital, Dordrecht, the Netherlands. Before referral for a PCN-procedure, patients were evaluated by a neurologist. In the work-up, patients underwent an MRI-scan of their cervical spine and a conventional X-ray aside from neurological examination. In order to be eligible for PCN, patients had to satisfy the following inclusion criteria: (1) have cervical radicular pain due to a disc herniation, which did not respond to conservative treatment; (2) have an MRI-confirmed contained, soft-disc herniation at levels C4 to C7. PCN was not performed if the following exclusion criteria were present: (1) previously performed surgery in the cervical spine area; (2) osteophytes or loss of more than 50% of disc height at the affected level as determined on conventional X-ray and (3) the concomitant myelopathy at the level of the disc herniation. The local institutional review board of the Albert Schweitzer Hospital, Dordrecht, the Netherlands approved the conduction of this study (MEC-2014.81). All patients gave written informed consent before filling in questionnaires. This study complies with the Declaration of Helsinki.

Surgical Procedure

In the Netherlands, PCN is performed by dedicated pain specialists. The step-by-step operative procedure of PCN has been published elsewhere.[12] In brief, PCN was performed under antibiotic prophylaxis and local anesthesia. After identifying the correct level of the cervical spine using fluoroscopy, an entry point for the needle was marked next to the medial part of the sternocleidomastoid muscle. After applying lidocaine locally, a needle and subsequently a trocar were inserted into the annulus fibrosis. After verifying the level of disc herniation again, the SpineWand (ArthroCare) was inserted and used for thermal ablation. After the ablation procedure, the instruments were removed, and a plaster was applied. Patients were discharged a few hours after surgery.

Outcomes and Outcome Collection

Through chart review, data on demographics and scores on the numeric rating scale (NRS) for arm pain and neck pain were collected retrospectively before surgery. Both NRSs were scored from 0 to 10 with '0' indicating no pain and '10' indicating the worst pain possible. The NRS is a valid and reliable Patient Reported Outcome Measure (PROM) in patients with cervical radiculopathy.[22] According to the local protocol, all patients had a short-term follow-up phone call scheduled 5 days after the PCN-procedure. During this phone call, the NRS for arm pain and neck pain were evaluated, and information regarding occurring reoperations or complications was collected. To measure long-term follow-up, patients received a questionnaire booklet containing the

Core Outcomes Measures Index (COMI) for the neck, questions regarding reoperations and occurrence of late complications and Likert-scales on recovery of symptoms and satisfaction with treatment with an informed consent form.[23] The COMI-neck is a seven-question survey, which measures five outcome domains, namely (neck and arm) pain, function, symptom-specific well-being, quality of life and disability on a scale from 0 to 10.[23] Based on these outcome domains, a summary score can be calculated in with a "0" indicating the "best score" and a "10" the "worst score".[23,24] If patients indicated in the questionnaire booklet that they had experienced any complication or underwent any reoperation, they were contacted by phone to clarify these. The Likert-scales on recovery and treatment satisfaction were 5-point Likert scales ranging from 'complete recovery' or 'very satisfied' to "made things worse" or "very dissatisfied". The COMI-neck is a valid and reliable PROM in patients with an indication for surgery due to cervical radiculopathy or myelopathy caused by degenerative disease.[23] Figure 1 depicts a graphical overview of the study procedures and the measurements performed.

Statistical Analysis

Categorical data were summarized with valid percentages (%); continuous data that are normally distributed are summarized with mean (standard deviation (SD)). Ordinal and non-normally distributed data are summarized with medians and interquartile ranges (IQRs). Normality was verified with Shapiro–Wilk Test. For the COMI-neck, no missing data were accepted for the individual items. Scores on the NRS for neck pain and arm pain were compared pre- and postoperatively using paired t-test. For analyzing purposes, the Likert-scales of the COMI-neck were dichotomized, meaning that the first two options were scored as a "good outcome" and the remaining three options as a "bad outcome". All analyses were conducted with SPSS version 27.0. A P value <0.05 indicated statistical significance.

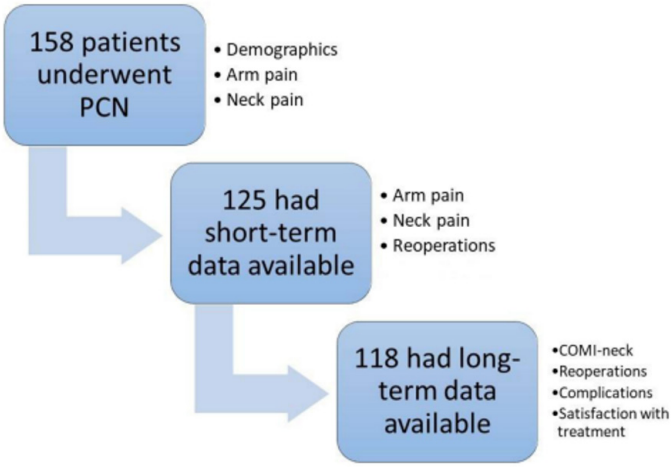

Figure 1: Graphical overview of the study and the measurements performed.

Results

Patients

In total 158 patients underwent PCN between 2010 and 2014. Figure 1 gives a graphic overview of the follow-up of the included patients. Short-term follow-up data were available for 79% (N = 125) of the patients, while long-term data were available for 75% (n = 118). Median duration of follow-up was 41.5 months (IQR 27.0 to 57.5). Table 1 gives an overview of the baseline demographics of the patients included. In brief, patients had a mean age of 47.3 ± 9.1, and a mean BMI of 26.6 ± 4.6. Furthermore, most disc herniations were located at C5-6 (48.1%) and C6-7 (48.1%). Prior to PCN, 43.0% of the patients had undergone physical therapy, 75.3% had received pain medication and 7.5% received transcutaneous electrical nerve stimulation. At baseline, the mean NRS for arm pain was 6.3 ± 2.5 and for neck pain 6.0 ± 2.7. Of the included patients, 62.7% had paresthesia, while 17.1% had subjective motor loss.

Clinical Outcomes at Short and Long-Term Follow-Up

Table 2 gives an overview of the long-term outcomes of arm pain and neck pain of the included patients. At short-term follow-up patients had a decrease in arm pain (difference of 3.0, 95% Confidence Interval (CI) 2.5 to 3.6, $p < 0.001$) compared to baseline (Table 2). This decrease was sustained at long-term follow-up (difference with baseline 2.8, 95% CI 1.9 to 3.6, $p < 0.001$). Neck pain showed similar decrease at short-term (2.8, 95% CI 2.3 to 3.3, $p < 0.001$) and long-term (2.7, 95% CI 1.9 to 3.5, $p < 0.001$) follow-up (Table 2). COMI-summary scores showed comparable results. On the Likert scale of recovery, eventually 67.8% of the patients had fully recovered of symptoms and 93.2% was still satisfied with the PCN-treatment results (Table 2).

Sex	*n=158*
Female [n,%]	84 (53.2%)
Male [n,%]	74 (46.8%)
Age [mean,SD]	47.3 ± 9.1
BMI [mean,SD]	26.6 ± 4.6
Level of disc herniation	*n=158*
C4-5 [n,%]	4 (2.5%)
C5-6 [n,%]	76 (48.1%)
C6-7 [n,%]	76 (48.1%)
C7-Th1 [n,%]	2 (1.3%)
Symptoms	*n=158*
Arm pain [mean,SD]	6.3 ± 2.5
Neck pain [mean,SD]	6.0 ± 2.7
Paresthesia [mean,SD]	99 (62.7%)
Subjective loss of motor function [mean,SD]	27 (17.1%)
Previous treatments	*n=158*
Pulsed radiofrequency [n,%]	37 (23.4%)
Epidural injections [n,%]	5 (3.2%)
Physical therapy [n,%]	68 (43.0%)
Pain medication [n,%]	119 (75.3%)
Transcutaneous electrical nerve stimulation [n,%]	12 (7.5%)

Abbreviations: n, number of participants, SD, Standard Deviation.

Table 1: Demographics and clinical characteristics of patinets who underwent cervical nuceloplasty treatment at baseline (N-158).

Surgical Outcomes and Complications

Table 3 gives an overview of the surgical outcomes and complications. At short-term follow-up, there were two cases of hoarseness (1.3%), 20 cases of dysphagia (12.7%), 3 cases of wound edema (1.9%) and one case of subcutaneous hematoma (0.6%). All complications are resolved spontaneously over time. At long-term follow-up, 24 patients (21.4%) underwent a reoperation of the cervical spine; 8 (6.8%) due to a disc herniation at another level and 16 (13.6%) due to a disc herniation at the same level as the PCN. Furthermore, 29.9% of the patients had no symptoms of cervical radicular pain at long-term follow-up. Neck pain, arm pain and sensory disturbances were the main complaints for 22.4% to 24.3% of the patients.

PROMs	Follow-up moment	Mean (SD)	Difference with baseline (95%CI)
NRS arm pain	Baseline	6.3 ± 2.5	
	Short-term	3.3 ± 2.7	3.0 (2.5 to 3.6)*
	Long-term	3.3 ± 3.0	2.8 (1.9 to 3.6)*
NRS neck pain	Baseline	6.0 ± 2.7	
	Short-term	3.4 ± 2.6	2.8 (2.3 to 3.3)*
	Long-term	3.1 ± 2.8	2.7 (1.9 to 3.5)*
COMI-neck			
Function	Long-term	3.6 ± 3.2	
Quality of life	Long-term	3.3 ± 2.4	
Summary score	Long-term	3.2 ± 2.5	
Recovered of symptoms	Long-term	80 (67.8%)	
Satisfied with treatment	Long-term	110 (93.2%)	

Abbreviations: PROMs, patient reported outcome measures, CI, Confidence Interval, SD, Standard Deviation, NRS, Numeratic Rating Scale, COMI-neck, * P<0.001.

Table 2: Clinical outcomes at short-term and long-term follow-up.

Complications	*n=143*
Hoarseness	2 (1.3%)
Dysphagia	20 (12.7%)
Wound edema	3 (1.9%)
Hematoma subcutaneous	1 (0.6%)
Main symptoms at long-term follow-up	*n=107*
None	32 (29.9%)
Neck pain	24 (22.4%)
Arm pain	25 (23.4%)
Paresthesia	26 (24.3%)
Underwent cervical disc surgery during long-term follow-up	*n=112*
No	88 (78.6%)
Yes, at a different level	8 (7.1%)
Yes, at the same level	16 (14.3%)

Table 3: Surgical outcomes and complications.

Discussion

Summary of Findings

The current study presents the results of a retrospective cohort study of 158 patients who underwent PCN due to cervical radicular pain caused by a disc herniation. At a median long-term follow-up of 41.5 months, data were available for 75% of the patients. PCN has a low complication risk, and all complications were transient. Based on the patient-reported outcomes, patients experienced a reduction of at least 2.7 on the NRS for arm pain and neck pain at both short- and longterm follow-up. This reduction in arm pain and neck pain exceeds commonly defined thresholds for minimally clinically important differences in the treatment of cervical radiculopathy.[25,26] A commonly mentioned concern of applying minimally invasive approaches is the limited working area required to remove enough tissue, and therefore a potential increased risk of recurrent disc herniation.

Comparison with Literature

In the literature, some studies can be identified measuring clinical outcomes or long-term data on PCN. In a retrospective cohort study of 69 patients, Halim et al looked at PROMs at a mean follow-up of 24 months.[16] Twenty-seven patients fulfilled ideal selection criteria for PCN, i.e. patients with a single-level contained cervical herniated disc, which did not resolve with conservative treatment, diagnosed on preoperative MRI and confirmed by a diagnostic selective nerve root block, and 42 patients did not meet these criteria.[16] Even though patients who fulfilled the ideal criteria were less likely to use medication postoperatively and were more likely to be satisfied with the treatment, no differences were found in pain scores or the neck disability index.[16] This study results suggest that perhaps more patients, than those that were deemed ideal, may benefit from a PCN treatment. Nevertheless, the results of Halim et al appear to be in line with the results of the current study. Aside from pain and our self-perceived success with interventions, the COMI-neck also measured symptom-specific well-being, quality of life, social disability and work disability. When we compare the results of these outcome domains of the current study, with the outcomes reported in observational studies among patients undergoing anterior cervical spine surgery, we can see comparable decreases in pain scores and the COMI-summary score, showing an overall increase in the different COMI-domains.[23,27] Kim et al also looked at predictors for the success of PCN.[16,17] In their retrospective study of 201 patients, factors such as unilateral radiculopathy and the use of a specific technique of PCN (curved-tip technique) were identified as predictors of success, while longer pain duration and concurrent spinal canal stenosis were identified as negative predictors. To be noted, the success rate of PCN was 66.7% in the study of Kim et al, though they used a more broader applied indication for PCN, their results appear to be in line with our study. Li et al published the results of a prospective study among 126 patients undergoing PCN for a symptomatic cervical disc herniation.[28] The procedure was successful for 83.7%

of the patients and pain treatment reached minimally clinical important differences. There was one case of a device, ie partial Perc-D Spine Wand, that broke in the disc space. The rate of recurrent disc herniations was zero, which was lower than in our case series. Perhaps, the length of follow-up in the study by Li et al,[28] i.e. 12 months, may explain the difference somewhat. In our study, a total of 16 (13.6%) patients underwent a revision procedure for a "recurrent" disc herniation at the index level at long-term follow-up. In other words, ACD(F) was prevented in 86.4% of the patients. This reoperation rate is comparable with the reoperation rates of ACDF, i.e. 7.8% to 15%.[29,30] Kessinger studied the rate of reoperation after PCN and identified a reoperation rate of 19.5% in his study population of 133 patients.[31] This rate appears to be somewhat higher than the rate we found in our study. This difference may be attributed to a difference in the length of the follow-up between both studies. However, it is up to debate how clinically important revision procedures are at, for instance, ten years of follow-up. Although our study did not have a control group, i.e. surgery or conservative therapy, there are studies who compared PCN with surgery. In a recently published randomized controlled trial, 48 patients with cervical radicular pain as a result of a single-level contained soft disc hernia were randomized between PCN and ACD.[21] In this study, it was shown that at short-term follow-up, i.e. 3 months, the ACD group performed significantly better on arm pain reduction than the PCN group. However, the difference between the groups was 17.2 mm on a VAS scale of 100 mm, this difference can be disputed for its clinical importance.[21] At long-term follow-up, i.e. one year after PCN, no significant differences between the groups were found, suggesting a place for PCN in the treatment of cervical radicular pain. Another recently performed RCT compared the effects of PCN to posterior decompression in 35 patients suffering from single-level disc-herniation with an indication for surgery.[32] In this trial, no significant differences were found between the groups on radicular arm pain and neck pain 3 and 6 months after the intervention. Finally, one study made a retrospective comparison in 50 patients who either underwent a PCN or a percutaneous cervical discectomy for a contained cervical disc herniation.[33] This study also showed that PCN had comparable results in terms of clinical success or complications, compared to cervical discectomy.

Strengths and Limitations

Advantages of this study are the long follow-up duration after treatment and the relatively large sample size of patients undergoing PCN. Another advantage of our study is the 25% of loss to follow-up at a median of 41.5 months seems to be comparable to the long-term follow-up rates of prospective studies (18% to 37% loss to follow-up).[34–36] Furthermore, missing data analyses suggest that data was missing completely at random and therefore we expect a low impact of the missing data on the study results. Finally, several studies show that the amount of missing data may not be related to the quality of the study.[37,38] Some limitations, however, must be acknowledged. First, it is the design of the study. Since this study is retrospective, recall bias might have been introduced. Furthermore, at baseline, only a selected number of variables were

available, such as pain scores. Another limitation may lie in the generalizability of the study results. PCN is only performed in patients with cervical radicular pain due to contained soft-disc herniations without the presence of osteophytes or significant loss of disc height. Therefore, PCN would only be a treatment alternative for a selected group of patients.

Implications

Based on our data, PCN appears to be a safe and effective treatment at short-term and long-term follow-up for primary patients with cervical radicular pain due to a contained soft-disc herniation. It prevented the need for ACD(F) in 86.4% of the patients, showing potency of PCN as a treatment option alongside ACD(F) to treat arm pain. Even though in our study population patients experienced a statistically significant decrease in neck pain, PCN is not recommended to be applied to solely treat neck pain in our practice. As aforementioned, PCN was only performed in a strongly selected patient population. Therefore, in our opinion ACD(F) will remain as the standard treatment in cases of osteophytes, myelopathy or other cases not suited for PCN. Another important area, which is underreported in the literature, is the cost-effectiveness. As PCN shows equivalent results to ACD on the short-term and long-term follow-up in the literature,[21,32] the height of the costs of the surgery, primary care, secondary care and work loss productivity will determine if PCN is cost-effective compared to ACD.

Conclusion

PCN appears to be a safe and effective treatment for a specific selection of cervical herniated discs, with an acceptable long-term reoperation rate. This study results suggest a potential role of PCN as a less invasive treatment option for cervical radicular pain due to a contained soft-disc herniation before surgery should be considered.

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REFERENCES

1. Bogduk N. On the definitions and physiology of back pain, referred pain, and radicular pain. Pain. 2009;147(1–3):17–19. doi:10.1016/j. pain.2009.08.020
2. Daffner SD, Hilibrand AS, Hanscom BS, Brislin BT, Vaccaro AR, Albert TJ. Impact of neck and arm pain on overall health status. Spine. 2003;28 (17):2030–2035. doi:10.1097/01.BRS.0000083325.27357.39
3. Sleijser-Koehorst MLS, Coppieters MW, Heymans MW, Rooker S, Verhagen AP, Scholten-Peeters GGM. Clinical course and prognostic models for the conservative management of cervical radiculopathy: a prospective cohort study. Eur Spine J. 2018;27(11):2710–2719. doi:10.1007/s00586-018-5777-8
4. Liu WJ, Hu L, Chou PH, Wang JW, Kan WS. Comparison of anterior cervical discectomy and fusion versus posterior cervical foraminotomy in the treatment of cervical radiculopathy: a systematic review. Orthop Surg. 2016;8(4):425–431. doi:10.1111/os.12285
5. Yang X, Janssen T, Arts MP, Peul WC, Vleggeert-Lankamp CLA. Radiological follow-up after implanting cervical disc prosthesis in anterior discectomy: a systematic review. Spine J. 2018;18(9):1678–1693. doi:10.1016/j.spinee.2018.04.021
6. Donk RD, Verbeek ALM, Verhagen WIM, Groenewoud H, Hosman AJF, Bartels R. What's the best surgical treatment for patients with cervical radiculopathy due to single-level degenerative disease? A randomized controlled trial. PLoS One. 2017;12(8):e0183603. doi:10.1371/journal. pone.0183603
7. Vleggeert-Lankamp CLA, Janssen TMH, van Zwet E, et al. The NECK trial: effectiveness of anterior cervical discectomy with or without interbody fusion and arthroplasty in the treatment of cervical disc herniation; a double-blinded randomised controlled trial. Spine J. 2018;19:965–975.
8. de Rooij JD, Gadjradj PS, Soria van Hoeve JS, Harhangi BS. Anterior cervical discectomy without fusion for a symptomatic cervical disk herniation. Acta Neurochir. 2017;159(7):1283–1287. doi:10.1007/s00701-017-3189-x
9. Nanda A, Sharma M, Sonig A, Ambekar S, Bollam P. Surgical complications of anterior cervical discectomy and fusion for cervical degenerative disk disease: a single surgeon's experience of 1576 patients. World Neurosurg. 2014;82(6):1380–1387. doi:10.1016/j.wneu.2013.09.022
10. Bovonratwet P, Fu MC, Tyagi V, et al. Incidence, risk factors, and clinical implications of postoperative hematoma requiring reoperation following anterior cervical discectomy and fusion. Spine. 2018;44:543–549.
11. Lykissas MG, Giannoulis D. Minimally invasive spine surgery for degenerative spine disease and deformity correction: a literature review. Ann Transl Med. 2018;6(6):99. doi:10.21037/atm.2018.03.18
12. Gadjradj PS, Rubinstein SM, Peul WC, et al. Full endoscopic versus open discectomy for sciatica: randomised controlled non-inferiority trial. BMJ. 2022;376:e065846. doi:10.1136/bmj-2021-065846
13. Gadjradj PS, Broulikova HM, van Dongen JM, et al. Cost-effectiveness of full endoscopic versus open discectomy for sciatica. Br J Sports Med. 2022. doi:10.1136/bjsports-2021-104808
14. de Rooij JD, Gadjradj PS, Soria van Hoeve JS, Huygen FJ, Aukes HA, Harhangi BS. Percutaneous nucleoplasty for the treatment of a contained cervical disk herniation. Clin Spine Surg. 2017;30(9):389–391. doi:10.1097/BSD.0000000000000583
15. Gerges FJ, Lipsitz SR, Nedeljkovic SS. A systematic review on the effectiveness of the Nucleoplasty procedure for discogenic pain. Pain Physician. 2010;13(2):117–132.
16. Halim W, Wullems JA, Lim T, et al. The long-term efficacy and safety of percutaneous cervical nucleoplasty in patients with a contained herniated disk. Pain Pract. 2013;13(5):364–371. doi:10.1111/papr.12003
17. Kim MK, Sim SE, Kim YC, et al. Predictive factors of successful percutaneous cervical nucleoplasty for the treatment of pain with cervical herniated disk. World Neurosurg. 2018;114:e654–e662. doi:10.1016/j.wneu.2018.03.046
18. Birnbaum K. Percutaneous cervical disc decompression. Surg Radiol Anat. 2009;31(5):379–387. doi:10.1007/s00276-009-0462-6
19. Cesaroni A, Nardi PV. Plasma disc decompression for contained cervical disc herniation: a randomized, controlled trial. Eur Spine J. 2010;19 (3):477–486. doi:10.1007/s00586-009-1189-0

20. Nardi PV, Cabezas D, Cesaroni A. Percutaneous cervical nucleoplasty using coblation technology. Clinical results in fifty consecutive cases. Acta Neurochir Suppl. 2005;92:73–78.
21. de Rooij J, Harhangi B, Aukes H, Groeneweg G, Stronks D, Huygen F. The effect of percutaneous nucleoplasty vs anterior discectomy in patients with cervical radicular pain due to a single-level contained soft-disc herniation: a randomized controlled trial. Pain Physician. 2020;23(6):553–564.
22. Young IA, Cleland JA, Michener LA, Brown C. Reliability, construct validity, and responsiveness of the neck disability index, patient-specific functional scale, and numeric pain rating scale in patients with cervical radiculopathy. Am J Phys Med Rehabil. 2010;89(10):831–839. doi:10.1097/PHM.0b013e3181ec98e6
23. Gadjradj PS, Chin-See-Chong TC, Donk D, Depauw P, Tulder MWV, Harhangi BS. Cross-cultural adaptation and psychometric validation of the Dutch version of the core outcome measures index for the neck in patients undergoing surgery for degenerative disease of the cervical spine. Neurospine. 2021;18(4):798–805. doi:10.14245/ns.2142682.341
24. Fankhauser CD, Mutter U, Aghayev E, Mannion AF. Validity and responsiveness of the Core Outcome Measures Index (COMI) for the neck. Eur Spine J. 2012;21(1):101–114. doi:10.1007/s00586-011-1921-4 25. Andresen AK, Paulsen RT, Busch F, Isenberg-Jorgensen A, Carreon LY, Andersen MO. Patient-reported outcomes and patient-reported satisfaction after surgical treatment for cervical radiculopathy. Global Spine J. 2018;8(7):703–708. doi:10.1177/2192568218765398
26. Parker SL, Godil SS, Shau DN, Mendenhall SK, McGirt MJ. Assessment of the minimum clinically important difference in pain, disability, and quality of life after anterior cervical discectomy and fusion: clinical article. J Neurosurg Spine. 2013;18(2):154–160. doi:10.3171/2012.10. SPINE12312
27. Staub LP, Ryser C, Röder C, et al. Total disc arthroplasty versus anterior cervical interbody fusion: use of the Spine Tango registry to supplement the evidence from randomized control trials. Spine J. 2016;16(2):136–145. doi:10.1016/j.spinee.2015.11.056
28. Li J, Yan DL, Zhang ZH. Percutaneous cervical nucleoplasty in the treatment of cervical disc herniation. Eur Spine J. 2008;17(12):1664–1669. doi:10.1007/s00586-008-0786-7
29. Emami A, Coban D, Changoor S, et al. Comparing mid-term outcomes between ACDF and minimally invasive posterior cervical foraminotomy in the treatment of cervical radiculopathy. Spine. 2021. doi:10.1097/BRS.0000000000004140
30. van Eck CF, Regan C, Donaldson WF, Kang JD, Lee JY. The revision rate and occurrence of adjacent segment disease after anterior cervical discectomy and fusion: a study of 672 consecutive patients. Spine. 2014;39(26):2143–2147. doi:10.1097/BRS.0000000000000636
31. Klessinger S. The frequency of re-surgery after cervical disc nucleoplasty. World Neurosurg. 2018;117:e552–e556. doi:10.1016/j.wneu.2018.06.075
32. Abrishamkar S, Salimi S, Pirmoradi H. Comparison the postoperation results of discectomy with nucleoplasty in single cervical disc herniation. Adv Biomed Res. 2018;7(1):29. doi:10.4103/abr.abr_159_15
33. Ierardi AM, Carnevale A, Cossu A, et al. Percutaneous cervical discectomy: retrospective comparison of two different techniques. Radiol Med. 2020;125(6):569–577. doi:10.1007/s11547-020-01133-x
34. Lequin MB, Verbaan D, Jacobs WC, et al. Surgery versus prolonged conservative treatment for sciatica: 5-year results of a randomised controlled trial. BMJ Open. 2013;3(5):e002534. doi:10.1136/bmjopen-2012-002534
35. Overdevest GM, Peul WC, Brand R, et al. Tubular discectomy versus conventional microdiscectomy for the treatment of lumbar disc herniation: long-term results of a randomised controlled trial. J Neurol Neurosurg Psychiatry. 2017;88(12):1008–1016. doi:10.1136/jnnp-2016-315306
36. Schenck CD, Terpstra SES, Moojen WA, et al. Interspinous process device versus conventional decompression for lumbar spinal stenosis: 5-year results of a randomized controlled trial. J Neurosurg Spine;2021. 1–9. doi:10.3171/2021.8.SPINE21419
37. Groves RM. Nonresponse rates and nonresponse bias in household surveys. Public Opin Q. 2006;70(5):646–675. doi:10.1093/poq/nfl033 38. Livingston EH, Wislar JS. Minimum response rates for survey research. Arch Surg. 2012;147(2):110.

Chapter nine

GENERAL DISCUSSION

Introduction

A small number of studies have shown that percutaneous cervical nucleoplasty (PCN), a minimally invasive treatment for cervical radicular pain (CRP) due to a disc herniation, is a safe and effective intervention, which can be performed on an outpatient basis with a short recovery time and no reported neurological complications associated with the procedure itself.[1-4] However, the quality of evidence is low because most of these studies have a non-randomized design. Moreover, the few identified randomized controlled trials (RCTs) are generally of poor methodological quality.[4] Although the primary outcomes of PCN are promising and its application is encouraged in well-selected cases (i.e., CRP as a result of minimally degenerated discs and discs with incomplete annular tears), more studies that are better designed are required.[4] It will be a significant improvement for patients if the same benefits of open surgery could be achieved with a minimally invasive intervention, such as PCN, without the serious complications of open surgery (e.g., symptomatic adjacent-level disease; pseudo-arthrosis; mechanical [device-related] failure; and ventral [approach-related] complications, such as dysphagia, hematoma, and recurrent laryngeal nerve palsy).[5-8] The overall aim of the work presented in this thesis was to gain a better insight into the efficacy and safety of PCN in comparison with other treatments for patients with CRP due to a single-level contained bulging disc herniation. In this chapter, we reflect on the key findings and clinical implications of this thesis.

Key findings and clinical implications

Chapter 2 presents a protocol in which we described, in detail, the process of preparing and maintaining a Cochrane systematic review to determine whether, for patients with herniated CRP, a PCN provides improved clinical and functional outcomes in comparison with other approaches that are frequently used. We compared PCN with no treatment, placebo treatment, conservative treatment (such as oral medications [e.g., steroidal anti-inflammatory drugs and muscle relaxants], physical therapy, manual therapy, bed rest, and cervical collars or tractions), nonsurgical procedures (e.g., pulsed radiofrequency of the dorsal root ganglion), and surgery (anterior and posterior decompression either through non-fusion techniques; fusion techniques via plate, cage, autograft, allograft material, or artificial disc; or a combination). The primary outcome measures were pain intensity in the arm and neck and neck-related functional status and recovery. The secondary outcome measures were global health status, work-related disability, psychosocial outcomes, and adverse effects.

Chapter 3 presents the results of a Cochrane systematic review in which we included two controlled clinical trials[1, 2] and four RCTs.[3, 9-11] All of the studies' participants were adults, who were aged from 16 to 65 years. Five studies included a homogeneous population of participants with a single-level contained herniated cervical disc that had

been proven through magnetic resonance imaging.[1, 3, 9, 11] Another study also included participants with a single-level contained herniated cervical disc; however, there was no mention of magnetic resonance imaging having been performed.[10] Three studies compared PCN with conservative treatment;[1-3] one study compared PCN with pulsed radiofrequency of the dorsal root ganglion;[9] and two studies compared PCN with surgery (i.e., anterior discectomy and open discectomy).[10, 11] Owing to the small number of included studies and lack of available data (i.e., most of the included studies used different clinical and functional outcomes), we could not pool all outcomes.

Compared with conservative treatment, the data suggest that PCN may reduce pain intensity and improve global health status and physical functioning in the long term (≥ 12 months) but not in the short term. Both of these results reached the threshold of clinical relevance. However, effect sizes were small, and the certainty of evidence varied from low to very low mostly because of the risk of bias and imprecision. For all of the other outcomes and comparisons, PCN may result in no to little differences because studies were too imprecise or poorly conducted. Larger, more well-designed RCTs with validated patient-reported outcome measures (PROMs) are required to evaluate the effect of PCN for clinical practice on patients with CRP due to a disc herniation. At present, there is only one other available systematic review that focuses on nucleoplasty treatment options for people with CRP due to a disc herniation. However, these authors did not use the gold standard (i.e., the grading of recommendations, assessment, development, and evaluation method)[12] to measure the quality of the evidence of the included trials and also included two controlled clinical trials as RCTs. Nevertheless, the findings are in line with our Cochrane review.

In **Chapters 4** and **5**, we describe the PCN technique and the anterior cervical discectomy (ACD) technique, which we used in our RCT. Both techniques are widely used in different ways. For instance, ACD with fusion (ACDF) is more universally accepted as a standard treatment for CRP due to a disc herniation, even though a cage is not routinely used in our center. Therefore, we clearly describe both interventional procedures in a step-by-step manner, which is safe, effective, and easily reproducible. In an accompanying video, two experienced specialists also identify and highlight specific nuances peculiar to these techniques.[13, 14]

In **Chapter 6**, we present the results of a survey on Dutch neurosurgeons' current management of a symptomatic cervical disc herniation. Of 134 surgeons, 96 (75.4%) participated in this survey. A total of 58.3% performed more than 50 cervical disc surgical procedures in the last five years. Of the frequently performed surgical procedures (i.e., ACD, ACDF, and dorsal cervical foraminotomy [DCF]), it was expected that ACDF be the most effective technique for arm pain in the short term (i.e., eight weeks) and long term (i.e., two years) by 57.4% and 52.7% of the respondents. Meanwhile, it was expected that DCF be the least effective, with 24.7% and 19.1% of the respondents expecting it

to result in the most arm pain in the short and long term, respectively. Furthermore, we found that the risks of recurrent radiculopathy in both the short and long term were expected to be highest after DCF (by 56.2% [short term] and 57.2% [long term] of the respondents) and lowest after ACDF (by 75.3% [short term] and 76.9% [long term] of the respondents). Though ACDF was the technique that was preferred the most, it was not expected that this technique would result in the lowest risk of complication. Almost 40% of the surgeons expected ACD to result in the lowest risk of complication (3.4%), whereas DCF (19.8%) and ACDF (15.2%) were expected to result in the highest risk of complication.

As is in line with our survey, ACDF is today the technique that is preferred the most for the treatment of CRP due to a single-level degenerative disc disease.[15, 16] The rationale of ACDF is to maintain cervical lordosis, avoid kyphotic deformation of the cervical spine, and prevent motion of the cervical spine so that arthrodesis can occur in a more stable environment.[17] However, compared with ACD, ACDF is associated with a number of drawbacks, including adjacent segment disease (i.e., degenerative changes that can occur on the discs and joints above or below the level where fusion surgery is performed), which becomes a major concern after fusion surgery.[16, 18, 19] In addition, ACDF has a significantly higher incidence of postoperative mechanical (device-related) complications, medical complications, and complications during reoperation.[19, 20] The 36-month incidence of reoperation in ACDF patients (10.5%) was almost twice that of ACD patients (5.7%), and of the patients who underwent reoperation, there was also an increase in the percentage of medical comorbidities in ACDF patients (25.65%) versus ACD patients (10%).[20] Furthermore, owing to the higher costs of the cage, ACDF is less cost-effective than ACD, despite the comparable effects.[20, 21] Additionally, two recently performed RCTs confirmed that ACD can provide a similarly adequate decompression of the affected cervical nerve root without the need for any implant.[7, 16] Based on this evidence, we state that instead of ACDF, ACD should be the preferred technique for the treatment of CRP due to a single-level degenerative disc disease. ACD provides a similarly adequate decompression to ACDF with a lower risk of complication and fewer costs.[7, 16, 20, 21]

In **Chapter 7**, we evaluate the effects of an RCT in which we compared PCN (n = 24) with ACD (n = 24) in patients with CRP due to a single-level contained bulging disc herniation. At three months, we observed a statistically significant interaction (group x time) between the groups in arm pain in favor of the ACD group. At 12 months, we observed a trend for greater improvement in arm pain in the ACD group. For all of the other outcome measures (i.e., intensity of arm pain at times of great effort, patient satisfaction, disability due to neck pain, and general health status), we did not observe any statistically significant interactions (group x time) at the three-month and 12-month follow-ups. As regards adverse effects, the PCN group did not experience any complication that was directly related to the procedure, which was in contrast to

the ACD group in which patients experienced some mild and transient complications, such as severe postoperative neck pain, dysphonia, and dysphagia. In the literature, only a few studies have evaluated the effects of PCN and ACD on patients with CRP due to single-level contained bulging disc herniation. A recently performed RCT[10] and a retrospective study[22] did not find statistical differences in pain reduction between PCN and ACD patients in time. At a short-term follow-up, our findings are in contrast with those of the RCT,[10] however, at a long-term follow-up (i.e., six months or later), the results of these studies[10, 22] might correspond to our trial results.

In our opinion, it is debatable whether the between-group difference in arm pain at the three-month follow-up (i.e., an average of 17.2 mm on a visual analog scale [VAS] of 0–100 mm) is clinically relevant. We searched the literature to interpret this between-group difference. However, there is no universally accepted mean difference in pain reduction between-group differences (i.e., treatment and comparator) in spine care, which makes it difficult to interpret RCTs and their implications for clinical practice.[25]

Evaluations of clinical importance must distinguish between the determining of mean improvements at the within-group and between-group levels.[23] The mean improvements within a group (i.e., the difference between endpoint and baseline within the group), which are important to patients, are known as the minimal clinically important change (MCIC). The mean improvements between groups at the end of a study, which are clinically important, are known as the minimal clinically important difference (MCID).[23, 24] In the literature, there is some consensus on the MCIC. Therefore, we decided to use the MCIC as a valuable measure to define the MCID. However, we realize that whether we can translate an MCIC one-on-one into an MCID is questionable.

There is some consensus that the MCIC for pain on a VAS ranges from 20 mm to 30 mm.[25-27] A clinical study with a study population fairly similar to ours (i.e., with patients undergoing cervical spine fusion because of degenerative conditions) found an MCIC of 25 mm for neck and arm pain.[27] We used the MCIC of this study[27] to determine the clinical relevance of the outcomes of the comparisons in our Cochrane review.[27] To direct the clinical relevance of our RCT, we used an MCIC of 30 mm.[25] At three months, our ACD patients showed a significantly greater reduction in the intensity of arm pain than the PCN patients, namely an average of 17.2 mm on a VAS of 100 mm. Although we opted for a slightly higher MCIC in this RCT, choosing an MCIC between 20 mm and 25 mm on a VAS of 100 mm would not have made a difference to the findings of our trial.

Recently, the Initiative on methods, measurement, and pain assessment in clinical trials (IMMPACT) group provided some guidance to interpret the clinical importance of between-group differences in an RCT.[24] The group suggests that a number of factors should be considered when evaluating the MCID. The first consideration is that there must be a statistically significant difference between the groups, which

is a necessary but insufficient criterion. In addition, the mean group difference with respect to the primary outcome variable can be compared with the effects associated with other treatments that are considered to have clinically important benefits. Other characteristics to consider include the safety of the treatment, the results for secondary efficacy outcomes (including physical and emotional functioning), and the limitations of existing treatments.[24] Another important area, which the IMMPACT group did not report, is the cost-effectiveness. As PCN shows results that are equivalent to those of ACD at the short-term and long-term follow-ups in the literature,[10, 11] the height of the costs of the surgery, primary care, secondary care, and a reduction in productivity (work loss) will also determine whether PCN is cost-effective when compared to ACD.

Another point of interest is that the careful selection of patients is important for a successful treatment with PCN.[28, 29] In particular, patients with incomplete annular tears and minimally degenerated discs may benefit the most from this technique.[2, 28, 29] However, at the start of our trial, it was not known that a shorter pain duration is a positive predictor of successful PCN.[29, 30] At baseline, the mean pain duration of our PCN group was 18.17 months, which fell within the range of the mean pain duration of patients with a negative outcome following the PCN procedure (10.85[30] to 37 months,[29] respectively). As far as we know, there are no studies that have examined the optimal timing for PCN. However, it is known that patients with a shorter pain duration (e.g., 6.75[30] to 16 months)[29] achieve better outcomes. Taking this knowledge into consideration, we conclude that the long mean pain duration of our PCN group at baseline may have negatively impacted the outcomes of our PCN group.

Another matter to consider is that this study was originally designed as a trial with three treatment groups: PCN, ACD, and physical therapy (PT). It turned out that almost all of the eligible patients refused to participate in the PT group because they had previously been unsuccessfully treated using PT. These patients preferred to be treated through PCN or ACD, which resulted in a slow inclusion rate in the PT group. Therefore, we withdrew the PT group from the trial. Hence, we could not compare PCN and ACD with conservative treatment. It would have been of great interest to compare the natural course of CRP due to single-level degenerative disease with PT to PCN and ACD because the effects of these three interventions have never before been compared in an RCT.

At follow-ups, the efficacy of PCN has been found to last from two months up to two years[1-3, 11, 29] however, long-term evidence on the effectiveness and safety of this technique is lacking. Therefore, in **Chapter 8**, we conduct a retrospective cohort study to evaluate the long-term clinical effects of PCN. In this study, we included 158 patients who underwent PCN between 2010 and 2014 with a median duration of follow-up of four years. At a short-term follow-up, data were available for 79% (n = 125) of the patients, while long-term data were available for 74.7% (n = 118). At the short-term follow-up, patients were experiencing less arm pain (a difference of 3.0, 95% confidence

interval [CI] 2.5 to 3.6, $p < 0.001$) than they were at baseline. This decrease was sustained at a long-term follow-up (difference with baseline 2.8, 95% CI 1.9 to 3.6, $p < 0.001$). At a short-term follow-up, there was a similar reduction in neck pain (2.8, 95% CI 2.3 to 3.3, $p < 0.001$) and at a long-term follow-up (2.7, 95% CI 1.9 to 3.5, $p < 0.001$; Table 2). On the Likert scale of recovery, 67.8% of the patients had eventually fully recovered from symptoms, and 93.2% remained satisfied with the PCN treatment results. These reductions in arm and neck pain exceed the commonly defined thresholds for MCIC in spine care, as we mentioned earlier in this discussion.

A commonly mentioned concern of adopting minimally invasive approaches is the limited working area to remove sufficient tissue, which therefore poses a potentially increased risk of recurrent disc herniation. In this study, 16 patients (13.6%) underwent reoperation for a "recurrent" disc herniation at the index level at the long-term follow-up. In other words, PCN prevented open surgery in 86.4% of the patients, which is comparable to the reoperation rates of ACDF (i.e., 7.8% to 15%).[31, 32] These findings emphasize the potency of PCN as a treatment option alongside (ACD)F for the treatment of arm pain. Although our patients in this study experienced a statistically significant reduction in neck pain, the use of PCN to solely treat neck pain is not recommended in our practice. As previously mentioned, PCN was only used in a strongly selected patient population. Therefore, in our opinion, ACD will continue to be the standard treatment in cases of osteophytes, myelopathy, or other cases that are not suited to PCN.

Strengths and limitations of this thesis

The strengths of this thesis were that we conducted the first RCT to gain a better insight into the efficacy and safety of PCN in comparison with surgery (ACD) for patients with CRP due to single-level contained bulging disc herniation by using validated PROMs. Using these validated PROMs will allow for an improvement in the quality of future research (e.g., systematic reviews) to further improve cervical spine care. Another of the thesis's strengths was that we also conducted the first Cochrane review to obtain more evidence as to whether PCN improves clinical and functional outcomes in comparison with surgery, nonsurgical interventions (pulsed radiofrequency), and conservative treatment for patients with CRP due to single-level disc herniation.

A limitation of this thesis was that in the conducted RCT, the inclusion of patients was ended before we reached the required sample size, and this was due to the limited number of eligible patients, which probably resulted in a heightened type II error and consequently a limitation of the internal validity of our study. However, we did discover a significant difference between the groups as regards reduction in the intensity of arm pain at the three-month follow-up.

Another limitation was that we had to withdraw our PT group from our RCT. It would have been of great interest to gain insight into the effect of PT in comparison to PCN and ACD, as these interventions have never before been compared in an RCT.

Another of this thesis's limitations was the lack of a universally accepted mean difference in pain reduction between-group differences (i.e., treatment and comparator) in spine care, which makes it difficult to interpret RCTs, systematic reviews, and their implications for clinical practice.

Recommendations for future research

Future research should focus, inter alia, on evaluating the optimal time frame for PCN. In addition, larger, more well-designed RCTs with validated PROMs are required to evaluate the efficacy of PCN in comparison to surgery and conservative treatment for clinical practice in patients with CRP due to a contained disc herniation. Lastly, we must reach a consensus on how to interpret the clinical relevance (i.e., the MCID) of RCTs and their implications for clinical practice in spinal care.

References

1. Nardi PV, Cabezas D, Cesaroni A. Percutaneous cervical nucleoplasty using coblation technology. Clinical results in fifty consecutive cases. Acta Neurochir Suppl. 2005;92:73-78.
2. Birnbaum K. Percutaneous cervical disc decompression. Surg Radiol Anat. 2009;31:379-387.
3. Cesaroni A, Nardi PV. Plasma disc decompression for contained cervical disc herniation: a randomized, controlled trial. Eur Spine J. 2010;19:477-486.
4. Wullems JA, Halim W, van der Weegen W. Current evidence of percutaneous nucleoplasty for the cervical herniated disk: a systematic review. Pain Pract. 2014;14:559-569.
5. Liu WJ, Hu L, Chou PH, Wang JW, Kan WS. Comparison of Anterior Cervical Discectomy and Fusion versus Posterior Cervical Foraminotomy in the Treatment of Cervical Radiculopathy: A Systematic Review. Orthop Surg. 2016;8:425-431.
6. Selvanathan SK, Beagrie C, Thomson S, Corns R, Deniz K, Derham C, et al. Anterior cervical discectomy and fusion versus posterior cervical foraminotomy in the treatment of brachialgia: the Leeds spinal unit experience (2008-2013). Acta Neurochir (Wien). 2015;157:1595-1600.
7. Vleggeert-Lankamp CLA, Janssen TMH, van Zwet E, Goedmakers CMW, Bosscher L, Peul W, et al. The NECK trial: Effectiveness of anterior cervical discectomy with or without interbody fusion and arthroplasty in the treatment of cervical disc herniation; a double-blinded randomised controlled trial. Spine J. 2018.
8. Hemmer C. Surgical Complications Associated With Cervical Spine Surgery. Orthop Nurs. 2018;37:348-354.
9. Halim W, van der Weegen W, Lim T, Wullems JA, Vissers KC. Percutaneous Cervical Nucleoplasty vs. Pulsed Radio Frequency of the Dorsal Root Ganglion in Patients with Contained Cervical Disk Herniation; A Prospective, Randomized Controlled Trial. Pain Practice. 2017;17:729-737.
10. Abrishamkar S, Salimi S, Pirmoradi H. Comparison the Postoperation results of Discectomy with Nucleoplasty in Single Cervical Disc Herniation. Adv Biomed Res. 2018;7:29.
11. de Rooij J, Harhangi B, Aukes H, Groeneweg G, Stronks D, Huygen F. The Effect of Percutaneous Nucleoplasty vs Anterior Discectomy in Patients with Cervical Radicular Pain due to a Single-Level Contained Soft-Disc Herniation: A Randomized Controlled Trial. Pain Physician. 2020;23:553-564.
12. Castellini G, Bruschettini M, Gianola S, Gluud C, Moja L. Assessing imprecision in Cochrane systematic reviews: a comparison of GRADE and Trial Sequential Analysis. Syst Rev. 2018;7:110.
13. de Rooij JD, Gadjradj PS, Soria van Hoeve JS, Harhangi BS. Anterior cervical discectomy without fusion for a symptomatic cervical disk herniation. Acta Neurochir (Wien). 2017;159:1283-1287.
14. de Rooij JD, Gadjradj PS, Soria van Hoeve JS, Huygen FJ, Aukes HA, Harhangi BS. Percutaneous Nucleoplasty for the Treatment of a Contained Cervical Disk Herniation. Clin Spine Surg. 2017;30:389-391.
15. Yang X, Janssen T, Arts MP, Peul WC, Vleggeert-Lankamp CLA. Radiological follow-up after implanting cervical disc prosthesis in anterior discectomy: a systematic review. Spine J. 2018;18:1678-1693.
16. Donk RD, Verbeek ALM, Verhagen WIM, Groenewoud H, Hosman AJF, Bartels R. What's the best surgical treatment for patients with cervical radiculopathy due to single-level degenerative disease? A randomized controlled trial. PLoS One. 2017;12:e0183603.
17. Nabhan A, Pape D, Pitzen T, Steudel WI, Bachelier F, Jung J, et al. Radiographic analysis of fusion progression following one-level cervical fusion with or without plate fixation. Zentralbl Neurochir. 2007;68:133-138.
18. Hashimoto K, Aizawa T, Kanno H, Itoi E. Adjacent segment degeneration after fusion spinal surgery-a systematic review. Int Orthop. 2018.
19. Epstein NE. A Review of Complication Rates for Anterior Cervical Diskectomy and Fusion (ACDF). Surg Neurol Int. 2019;10:100.

20. Radcliff K, Zigler J, Zigler J. Costs of cervical disc replacement versus anterior cervical discectomy and fusion for treatment of single-level cervical disc disease: an analysis of the Blue Health Intelligence database for acute and long-term costs and complications. Spine (Phila Pa 1976). 2015;40:521-529.
21. Lewis DJ, Attiah MA, Malhotra NR, Burnett MG, Stein SC. Anterior surgical management of single-level cervical disc disease: a cost-effectiveness analysis. Spine (Phila Pa 1976). 2014;39:2084-2092.
22. Yan D, Li J, Zhu H, Zhang Z, Duan L. Percutaneous cervical nucleoplasty and percutaneous cervical discectomy treatments of the contained cervical disc herniation. Arch Orthop Trauma Surg. 2010;130:1371-1376.
23. Ruyssen-Witrand A, Tubach F, Ravaud P. Systematic review reveals heterogeneity in definition of a clinically relevant difference in pain. J Clin Epidemiol. 2011;64:463-470.
24. Smith SM, Dworkin RH, Turk DC, McDermott MP, Eccleston C, Farrar JT, et al. Interpretation of chronic pain clinical trial outcomes: IMMPACT recommended considerations. Pain. 2020;161:2446-2461.
25. Lee JS, Hobden E, Stiell IG, Wells GA. Clinically important change in the visual analog scale after adequate pain control. Acad Emerg Med. 2003;10:1128-1130.
26. Ostelo RW, de Vet HC. Clinically important outcomes in low back pain. Best Pract Res Clin Rheumatol. 2005;19:593-607.
27. Carreon LY, Glassman SD, Campbell MJ, Anderson PA. Neck Disability Index, short form-36 physical component summary, and pain scales for neck and arm pain: the minimum clinically important difference and substantial clinical benefit after cervical spine fusion. Spine J. 2010;10:469-474.
28. Gerges FJ, Lipsitz SR, Nedeljkovic SS. A systematic review on the effectiveness of the Nucleoplasty procedure for discogenic pain. Pain Physician. 2010;13:117-132.
29. Halim W, Wullems JA, Lim T, Aukes HA, van der Weegen W, Vissers KC, et al. The long-term efficacy and safety of percutaneous cervical nucleoplasty in patients with a contained herniated disk. Pain Pract. 2013;13:364-371.
30. Kim MK, Sim SE, Kim YC, Kim JS, Kwon SM, Yoo Y, et al. Predictive Factors of Successful Percutaneous Cervical Nucleoplasty for the Treatment of Pain with Cervical Herniated Disk. World Neurosurg. 2018;114:e654-e662.
31. Emami A, Coban D, Changoor S, Dunn C, Sahai N, Sinha K, et al. Comparing Mid-Term Outcomes Between ACDF and Minimally Invasive Posterior Cervical Foraminotomy in the Treatment of Cervical Radiculopathy. Spine (Phila Pa 1976). 2021.
32. van Eck CF, Regan C, Donaldson WF, Kang JD, Lee JY. The revision rate and occurrence of adjacent segment disease after anterior cervical discectomy and fusion: a study of 672 consecutive patients. Spine (Phila Pa 1976). 2014;39:2143-2147.

Chapter ten

SUMMARY

English summary

Cervical radicular pain (CRP) due to a disc herniation is a common condition, which, with neurological disorders, can be extremely painful and largely impact one's daily functioning and quality of life. A wide range of nonsurgical and surgical interventions are used with major impacts on direct and indirect healthcare costs, making it a highly relevant topic. A relatively new minimally invasive approach (i.e., nucleoplasty) is becoming increasingly popular among interventional pain specialists as one of the therapeutic options for the treatment of CRP due to a disc herniation. This thesis focuses on the efficacy and safety of this new treatment option in comparison to conservative and surgical treatments for patients with CRP due to a disc herniation.

This thesis can be divided in three parts after the general introduction in **chapter 1**.

Part I focuses on identifying, evaluating, and summarizing the results of (non) randomized studies and compares percutaneous cervical nucleoplasty (PCN) with other treatments for patients with CRP due to a disc herniation.

Chapter 2 presents a Cochrane protocol in which we described, in detail, the process of conducting and maintaining a Cochrane systematic review on the effects of PCN in comparison with other treatments for patients with CRP due to a disc herniation.

Chapter 3 describes the results of a Cochrane systematic review. Multiple online databases were systematically searched for the purpose of including eligible studies up to October 2021. We included four RCTs (224 participants) and two non-RCTs (129 participants) of patients with CRP due to a disc herniation. The risk of bias was high in all RCTs and "critical" in the two non-RCTs, which were consequently excluded from the analyses. Summarizing the evidence reveals that evidence that PCN may reduce pain intensity and improve global health status and physical functioning in the long term in comparison with conservative treatment is of low quality. However, both of these aforementioned outcomes reached the threshold of clinical relevance. For all of the other outcomes and comparisons, the quality of evidence ranged from low to very low.

Part II of this thesis focuses on describing the intervention techniques that we used in our RCT because both of these techniques (PCN and ACD), are used differently worldwide. We also investigated Dutch neurosurgeons' treatment preferences for the management of symptomatic disc herniation.

In **Chapters 4** and **5**, we describe our RCT's PCN technique and the anterior cervical discectomy (ACD) technique in a step-by-step manner that is safe, effective, and easily reproducible. In an accompanying video, two experienced specialists also identify and highlight specific nuances of these techniques.

Chapter 6 presents the results of a survey on 134 Dutch neurosurgeons' management of patients with a cervical disc herniation (CDH). For 76.3% of these neurosurgeons, anterior cervical discectomy with fusion (ACDF) was the preferred procedure to treat CDH. Despite a lack of evidence, it was expected that ACDF would have the highest effectiveness on radicular arm pain, as well as a greater risk of complication than ACD. Most of the neurosurgeons (47.9%) considered a minimum duration of eight to 12 weeks of radicular arm pain to be the optimal timing to perform CDH surgery. As regards the risk of recurrent CDH, it was expected that dorsal cervical foraminotomy would result in the highest risk and that ACDF would result in the lowest risk. Whether to fuse or not to fuse remains a controversial topic in degenerative spinal surgery. This study emphasizes the need to collect higher-quality evidence of optimal surgical management for CDH.

Part III of this thesis focuses on the results of our RCT and the long-term effects of PCN on patients with CRP due to a disc herniation.

Chapter 7 presents the results of an RCT in which we compared the effects of PCN (*n* = 24) and ACD (*n* = 24) on a group of patients with CRP due to a single-level contained soft-disc herniation. The primary outcome measure was intensity of arm pain, which was measured using a visual analog scale. Secondary outcome measures were intensity of arm pain at times of great effort, neck pain, global perceived effect, disability (neck disability index), and the patients' general health (Short Form Generated Health Survey [SF-36]). All outcome parameters were measured at baseline, after three months, and one year after intervention. At three months, we observed a statistically significant interaction (group x time) between the groups in the primary outcome measure, arm pain, in favor of the ACD group. However, it is debatable whether a mean difference of 17.2 mm on a visual analog scale of 100 mm in favor of the ACD group is clinically relevant. After a 12-month follow-up, no statistically significant differences in the other outcome parameters were observed between the groups. Therefore, we conclude that in the long term, PCN may be a good alternative to ACD for this group of patients.

Chapter 8 presents a single-center retrospective cohort study in which we evaluated the long-term clinical effects of PCN on 158 patients with CRP due to a contained soft-disc herniation.

Before surgery and five days after surgery, a pain score (numerical rating scales for arm and neck pain) and data on complications were collected. To determine long-term follow-up outcomes, patients were sent a questionnaire containing the core outcome measures: neck index, numerical rating scales for arm and neck pain, patient satisfaction Likert scales, and questions regarding the incidence of reoperations and complications. The median duration of follow-up was four years. At a short-term follow-up (i.e., five days after the PCN procedure) and a long-term follow-up, patients experienced a significant and clinically relevant reduction in arm pain in comparison

to their levels of arm pain at baseline. At the long-term follow-up, 67.8% of the patients had fully recovered from all of their symptoms, and 93.2% remained satisfied with the results of the PCN procedure. The percentage of reoperations for recurrent disc herniation was 21.4% at the long-term follow-up. Therefore, we conclude that with an acceptable long-term reoperation rate for patients with CRP due to a contained soft-disc herniation, PCN is a safe and effective treatment for the short-term and long-term follow-ups. These study results suggest the potential role of PCN as a less invasive treatment option before ACD should be considered for this group of patients.

Chapter 9, the final chapter of this thesis, discusses the main findings of this thesis, addresses the study limitations, and considers various implications for daily practice and future research.

Conclusion

When conservative treatment fails and before ACD should be considered, PCN can be a safe and effective treatment for well-selected patients with CRP due to a single-level contained bulging disc herniation. In our view, ACD will continue to be the standard treatment in cases of osteophytes, myelopathy, or other cases that are not suited to PCN.

Nederlandse samenvatting

Cervicaal radiculaire pijn (CRP) als gevolg van een hernia is een veel voorkomende neurologische aandoening. Het kan veel pijn geven en grote gevolgen hebben op het dagelijkse functioneren en kwaliteit van leven van de patiënt. Een breed scala aan niet chirurgische- en chirurgische behandelingen worden toegepast, welke een grote impact hebben op de (in)directe zorgkosten, hetgeen CRP tot een belangrijk maatschappelijk onderwerp maakt. Onder de interventionele pijnspecialisten is een relatief nieuwe minimaal invasieve interventie, namelijk percutane cervicale nucleoplasty, populair geworden als één van de behandelopties voor CRP als gevolg van een hernia. Dit proefschrift richt zich op de werkzaamheid en veiligheid van deze nieuwe behandeloptie in vergelijking tot niet chirurgische- en chirurgische behandelingen van patiënten met CRP als gevolg van een hernia.

Dit proefschrift kan in drie delen verdeeld worden na de algemene inleiding in **hoofdstuk 1**.

Deel I richt zich op het identificeren, evalueren en samenvatten van de resultaten van (niet) gerandomiseerde studies waarin percutane cervicale nucleoplasty (PCN) wordt vergeleken ten opzichte van andere behandelingen bij patiënten met CRP als gevolg van een hernia.

Hoofdstuk 2 presenteert een Cochrane-protocol waarin we in detail het proces beschrijven van het uitvoeren van een systematische Cochrane review over de effecten van PCN in vergelijking met andere behandelingen bij patiënten met CRP als gevolg van een hernia.

Hoofdstuk 3 beschrijft de resultaten van een Cochrane review waarin op een systematische wijze verschillende online databases tot en met 21 oktober 2021 zijn doorzocht. Uiteindelijk hebben we methodologisch vier gerandomiseerde studies (224 deelnemers) en twee niet-gerandomiseerde studies (129 deelnemers) van patiënten met CRP als gevolg van een hernia beoordeeld. Alle gerandomiseerde studies hadden een hoog risico op bias. De twee niet-gerandomiseerde studies hadden een zeer kritiek risico op bias en zijn daarom niet meegenomen in de analyse. Ten opzichte van conservatieve behandeling kunnen we stellen dat de kwaliteit van bewijs dat PCN op lange termijn tot minder pijn en een betere gezondheidstoestand op fysiek functioneren kan leiden laag is. Echter, deze beide uitkomstmaten bereikten wel klinische relevantie. De kwaliteit van bewijs van PCN ten opzichte van de andere uitkomstmaten en vergelijkingen was laag tot zeer laag.

Deel II van dit proefschrift richt zich op het duidelijk beschrijven van de interventietechnieken die we in onze gerandomiseerde studie hebben gebruikt, dit

omdat beide technieken wereldwijd verschillend worden toegepast. Ook hebben we de voorkeur van de behandeling van een symptomatische nekhernia onder neurochirurgen in Nederland onderzocht.

In **Hoofdstuk 4** hebben we de PCN techniek en in **Hoofdstuk 5** de anterieure cervicale discectomie (ACD) techniek van onze gerandomiseerde studie op een stapsgewijze manier beschreven die veilig, effectief en gemakkelijk reproduceerbaar is. In een begeleidende video hebben twee ervaren specialisten ook de specifieke nuances van beide technieken toegelicht.

Hoofdstuk 6 presenteert de resultaten van een onderzoek naar de behandeling van patiënten met een symptomatische nekhernia onder 134 Nederlandse neurochirurgen. Onder deze neurochirurgen (76,3%) was de anterieure cervicale discectomie met fusie techniek (ACDF) de voorkeurs behandeling van een symptomatische nekhernia. Ondanks wetenschappelijk gebrek aan bewijs, werd verwacht dat ACDF het meest effectief was op radiculaire arm pijn, maar ook dat deze techniek een hoger risico op complicaties had in vergelijking tot ACD. Een minimale duur van 8 tot 12 weken van pijn in de radiculaire arm werd door de meerderheid van de neurochirurgen (47,9%) als de optimale tijd beschouwd om een operatie voor een symptomatische nek hernia uit te voeren. Wat betreft het risico op een recidief van een nek hernia, werd verwacht dat een dorsale cervicale foraminotomie het hoogste risico opleverde en een ACDF het laagste risico. Wel of niet fuseren blijft een controversieel onderwerp bij degeneratieve wervelkolom chirurgie. Deze studie benadrukt de noodzakelijkheid naar het verzamelen van hogere kwaliteit van bewijs van de optimale tijd voor chirurgie bij een symptomatische nekhernia.

Deel III richt zich op de resultaten van onze gerandomiseerde studie en de lange termijn effecten van PCN bij patiënten met CRP als gevolg van een hernia.

Hoofdstuk 7 presenteert de resultaten van een gerandomiseerde studie waarin we de effecten van PCN (n=24) hebben vergeleken ten opzichte van ACD (n=24) bij patiënten met CRP veroorzaakt door een nekhernia. De primaire uitkomstmaat van deze studie was de intensiteit van armpijn, gemeten met een visueel analoge schaal (VAS). Secundaire uitkomsten waren de intensiteit van armpijn tijdens zware inspanning, nekpijn, mate van herstel na behandeling, dagelijkse beperkingen bij nekklachten en de gezondheidstoestand (SF-36) van de patiënt. Alle uitkomstmaten werden gemeten vlak voor de start van de behandeling, drie maanden en een jaar na de behandeling. Na drie maanden vonden we een statistisch significante interactie (groep x tijd) op de primaire uitkomstmaat armpijn ten voordele van de ACD groep. Echter, het valt te bediscussiëren of een gemiddeld verschil van 17.2 mm op een VAS-score van 100 mm ten voordele van de ACD groep klinisch relevant is. Na een jaar werden op de andere uitkomstmaten geen statistische significante interacties tussen de groepen meer gevonden. Daarom

concluderen wij dat op de langere termijn, PCN een goed alternatief kan zijn voor ACD bij deze groep patiënten.

Hoofdstuk 8 bevat de resultaten van een retrospectieve cohortstudie van één perifeer ziekenhuis waarin we de klinische lange termijn resultaten van PCN bij 158 patiënten met CRP als gevolg van een hernia onderzocht hebben. Voor de operatie en vijf dagen na de operatie werd een pijnscore (NRS) van arm- en nekpijn gevraagd en gegevens over complicaties verzameld. Om de resultaten van PCN op de lange termijn te bepalen kregen de patiënten een vragenlijst toegestuurd met vragen over pijnscores (NRS) voor arm- en nekpijn, Likert schalen over patiënttevredenheid en vragen over de incidentie van heroperaties en complicaties. De mediane duur van follow-up van patiënten was 4 jaar. Op zowel de korte termijn, d.w.z. vijf dagen na de PCN procedure, en de lange termijn ervaarden de patiënten een significante en klinisch relevante afname van arm pijn ten opzichte van voor de operatie. Op de lange termijn was 67,8% van de patiënten volledig hersteld van alle symptomen en bleef 93,2% tevreden met de resultaten van de PCN-procedure. Het percentage her operaties voor een recidief van een nekhernia was op de lange termijn 21,4 %. Daarom concluderen we dat PCN een veilige en effectieve behandeling is voor zowel de korte- als lange termijn en dat PCN een acceptabel percentage her operaties heeft op de lange termijn. Deze onderzoeksresultaten impliceren een potentiele rol van PCN als een minder invasieve behandelingsoptie, voordat ACD bij deze groep patiënten moet worden overwogen.

Hoofdstuk 9, het laatste hoofdstuk van dit proefschrift, bespreekt de belangrijkste bevindingen van dit proefschrift, behandelt de studiebeperkingen en behandelt verschillende implicaties voor de dagelijkse praktijk en toekomstig onderzoek.

Conclusie

Wanneer conservatieve behandeling faalt, kan PCN een veilige en effectieve behandeling zijn bij zorgvuldig geselecteerde patiënten met CRP als gevolg van een nekhernia, voordat ACD moet worden overwogen. Naar onze mening zal ACD de standaardbehandeling blijven in gevallen van osteofyten, myelopathie of andere situaties die niet geschikt zijn voor PCN.