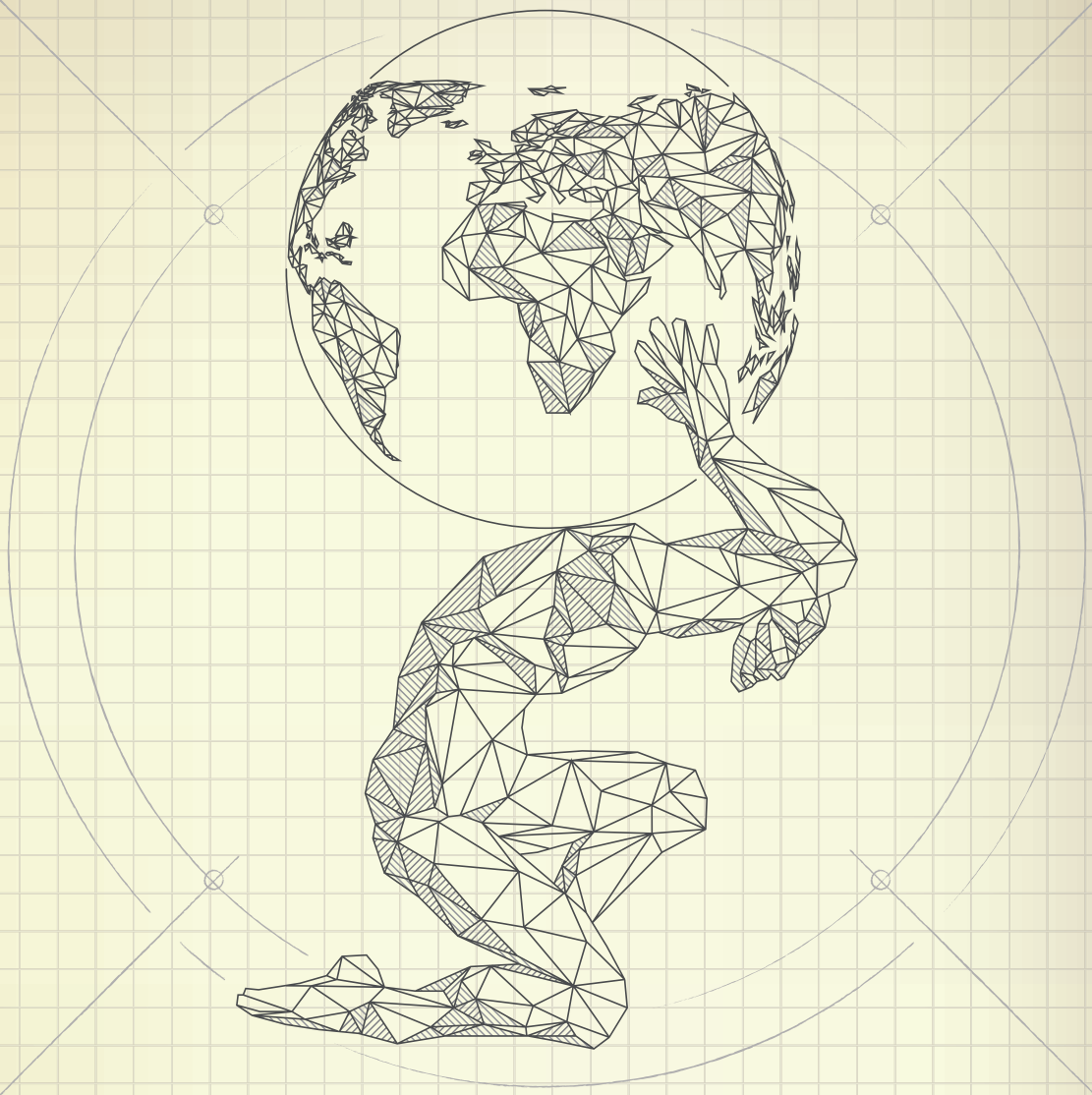
Motion preservation in cervical prosthesis surgery: Implications for adjacent segment degeneration

Yang, X.



Motion Preservation in Cervical Prosthesis Surgery

Implications for Adjacent Segment Degeneration

Xiaoyu Yang

MOTION PRESERVATION IN CERVICAL PROSTHESIS SURGERY
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MOTION PRESERVATION IN CERVICAL PROSTHESIS SURGERY
Implications for Adjacent Segment Degeneration

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	Prof.dr. H. van Santbrink	(Maastricht University)
	Dr. A. MacDowall	(Uppsala University)

Dedicated to my parents

For their endless love, support and encouragement

CONTENTS

Chapter 1

Introduction & Outline of the thesis

INTRODUCTION

Cervical radiculopathy is a frequently occurring neurologic disorder[1]. It was first described as a clinical diagnosis by Parkinson in 1817[2], although he ascribed it to 'rheumatic affection of the deltoid muscle'. Elliott then described how radicular symptoms might arise through narrowing of intervertebral foramina secondary to arthritic changes of the cervical spine in 1926[3]. In 1936, Turner and Oppenheimer described that intervertebral foraminal narrowing was caused by 'thinning' of the disc[4]. Nowadays, the clinical symptoms of cervical radiculopathy are considered to be characterized by radiating pain in the arm and/or fingers corresponding to the dermatome involved[5]. Generally, the symptoms are caused by spinal nerve root compression, which is usually attributable to disc herniation or spondylosis. The annual incidence rate of cervical radiculopathy indicated by a population-based study from Rochester, Minnesota, is 107.3 per 100,000 for men and 63.5 per 100,000 for women, with a peak of 202.9 per 100,000 persons for the age group of 50-54 years[2].

Although there are no universally accepted diagnosis criteria for cervical radiculopathy[6], the clinical diagnosis is based on the information collected from the medical history and physical examination. The cause of the radiculopathy can be compression of the spinal nerve root and this can be identified by diagnostic imaging (MRI) or supported by surgical findings[7]. In recent years, the understanding concerning the pathology, aetiology and implications regarding the treatment for cervical radiculopathy has increased[5,8-10]. The majority of patients has a favourable outcome with conservative treatment[2]. Usually, a wait and see policy in which the patients are treated with analgesics is successful[11]. In addition, physiotherapy is recommended to be effective for the treatment of neck pain[12]. Kuijper et al.[5] conducted a prospective, randomised controlled trial among patients with less than one month of symptoms of cervical radiculopathy, and demonstrated that the neck and arm pain reduced significantly for the patients with a semi-hard cervical collar and three to six weeks rest or physiotherapy with six-week home exercises compared with the wait and see policy.

The role of epidural injections is controversial. Some studies reported a favourable outcome with translaminar and transforaminal epidural injections of corticosteroids[13,14]. The complications, however, can be serious, including severe neurologic sequelae from brainstem and spinal cord infarction[15].

If patients are unresponsive to conservative treatment, surgical intervention may be considered. Surgical treatment of cervical radiculopathy has become more common and this led to an increase in the number of surgeries in treatment of cervical radiculopathy[8,10,16,17]. The surgical approach can be divided into posterior procedures, anterior procedures or a combination of these. In the first half of the last century, only posterior surgery was performed for cervical spinal pathologies. In the 1940s, posterior foraminotomy was introduced for managing cervical radiculopathy[18,19]. Subsequently, the popularity of the anterior approach for discectomy and fusion has increased because this approach avoids exposure of the spinal

canal and results in less soft tissue damage[20]. In the 1950s, anterior cervical discectomy was described with the use of autologous iliac crest interbody bone graft (ACDF) to result in reliable fusion rate and generally maintain spinal structural integrity[21-23]. However, in 1961, Hirsch debated the necessity of interbody fusion[24]. Anterior cervical discectomy (ACD) is the basic surgical treatment of patients with radicular pain caused by cervical disc herniation. The purpose of ACD is removal of the intervertebral disc in order to decompress the nerve root and alleviate radicular pain. However, cervical instability and segmental collapse with recurrent radicular pain has been documented after anterior discectomy. At present, ACDF is defined as the gold standard for cervical disc herniation since clinical researchers have demonstrated excellent clinical outcome with low complication rates in long term follow-up. The procedure remained largely unchanged until the 1990s. Cages and allograft bone were introduced to reduce the complications of harvesting autologous bone graft from the iliac crest. To decrease the prevalence of pseudarthrosis, plates were successfully introduced[25-27].

Frequently, surgeons perform ACDF to maintain disc height and cervical alignment, and to promote bony fusion to prevent instability. However, arthrodesis of a motion segment leads to increased mechanical load and stress at the levels adjacent to the fusion site. Therefore, the concept of accelerated adjacent segment degeneration (ASD) is proposed and widely discussed. Hilibrand et al.[28] reported a large retrospective study of patients who underwent ACDF. Symptomatic ASD occurred at a relative constant incidence of 2.9% annually. They predicted that 25.6% of the patients would have new disease at the adjacent level within 10 years after the operation[28]. This finding was generally considered with sepsis since it was not the experience that patients that had once had an ACDF regularly returned with radiculopathy at the adjacent level. Since Hillibrand et al. did not give insight in baseline degeneration data, it was thought that the changes diagnosed at 10-year follow-up were already present at baseline. Moreover, Hillibrand et al. reported that symptomatic ASD was less in patients who had ACDF at two levels. This finding supports the thought that baseline degeneration plays an important role.

Goffin et al. showed 92% additional radiological degeneration at the adjacent disc levels at late follow-up after ACDF[29], but they failed to demonstrate the clinical implication of radiological degenerative findings. Gore evaluated 200 asymptomatic persons radiographically. At 10 years follow-up, he showed new or progressive degenerative changes in 100 of the 159 participants (63%), but only 15% of patients reported pain in neck or arm, and only one patients actually underwent surgery for cervical radiculopathy[30].

These results suggest that the occurrence of degeneration at the adjacent levels is a physiological process, which is only natural to occur in patients upon aging. In absence of clinical complaints that can be attributed to the degeneration at the adjacent level, they should not be considered a complication of interbody fusion. To confirm this suggestion, investigating the relationship between radiological findings and clinical outcome is needed.

Instead of further investigating the relation between radiological findings and clinical symptoms, a new device was introduced to prevent accelerated ASD. And in the process of finding a market for this new device, the cervical disc prosthesis (ACDA), radiological findings were stressed to convince the surgeons to switch the ACDF procedure to the ACDA procedure. To prevent accelerated ASD, the cervical prosthesis was developed to maintain segmental range of motion (ROM) as well as to restore disc height, and thereby avoid neck pain and disability in post-surgical follow-up[31].

In this thesis we will use the results that are delivered by trials with the prosthesis to do what should have been done initially, namely, to investigate the correlation between radiological and clinical data in the follow up of anterior discectomy surgery.

The Netherlands Cervical Kinematics (NECK) trial is a multicentre prospective randomized controlled trial among patients with single level cervical radiculopathy due to a herniated disc, which was performed in Leiden University Medical Centre, Haaglanden Medical Centre and Alkmaar Medical Centre in the Netherlands. In the NECK trial, the effectiveness of ACDA was compared to ACD as well as to ACDF with a two-year follow-up[32]. It was shown that ACDA did not demonstrate a superior clinical outcome[33]. In the Radboud University Medical Centre, Nijmegen, the PROCON trial was performed with similar design and objectives, and a comparable clinical outcome was demonstrated between ACDA and ACD with or without fusion[34]. The radiological and clinical findings of these NECK trial and PROCON trial will be used to elaborate on the correlation between the two.

OBJECTIVES AND OUTLINE OF THIS THESIS

The main objective of this thesis is to unravel the relationship between radiological findings and clinical outcome in patients who were subjected to surgery for cervical radiculopathy via an anterior approach.

The first objective of this study is to summarize the radiological evaluation methods and outcome data that are described in literature (**chapter 2**). In spite of being scientifically debated, MRI is frequently prescribed in patients with cervical radiculopathy who are unresponsive to conservative treatment. **Chapter 3** reports on the correlation between the size of cervical disc herniation and clinical condition.

In **chapter 4**, data are presented on the occurrence of ASD in patients from the NECK and PROCON trial. The incidence of radiological ASD is compared between patients who underwent cervical arthroplasty and those who underwent arthrodesis. Subsequently, these ASD data were correlated to the ROM of the cervical spine before and after the three different forms of surgery. Not only was the influence of the surgical intervention regarding the ROM studied on the index level, but also with regard to the ROM of the total cervical spine (**chapter 5**).

Sagittal alignment of the cervical spine may be influenced by anterior cervical spine surgery. Altered sagittal alignment due to anterior discectomy may influence ASD. Therefore, cervical spine balance parameters, will be correlated to observed ASD in patients from the NECK and PROCON trial (**chapter 6**).

In the search for causes of (accelerated) degenerative changes in patients with radiculopathy, Modic vertebral end-plate signal changes visualized by MRI have been proposed as a possible cause. In **chapter 7**, a literature overview is presented of the association between clinical symptoms and Modic changes and cervical disc degeneration. In **chapter 8**, the results of NECK and PROCON trial are reported on the incidence of Modic changes and the observed correlation between the presence of Modic changes and radiological degeneration in cervical radiculopathy.

Heterotopic ossification has been reported as the adverse outcome after cervical arthroplasty, which counteracts motion preservation. In **chapter 9**, the occurrence and progression of heterotopic ossification is reported in the patients from the NECK and PROCON trial. The correlations between high grade heterotopic ossification, ROM and clinical outcome is studied.

Finally, the clinical and radiological outcome data of the two different cervical disc prostheses used in the NECK and PROCON trial are compared (**chapter 10**).

Discussions and conclusions with regard to the results are presented in **chapter 11**. The dissertation is concluded with a summary in **chapter 12**.

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Chapter 2

Radiological Follow-up after Implanting Cervical Disc Prosthesis in Anterior Discectomy: A Systematic Review

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ABSTRACT

Objective

The objective of this study was to review current literature on comparison of radiological outcome of cervical arthroplasty with fusion after anterior discectomy for radiculopathy.

Methods

A literature search was performed in PubMed, Embase, Web of Science, COCHRANE, CENTRAL and CINAHL using a sensitive search string combination. Studies were selected by predefined selection criteria (patients exclusively suffering from cervical radiculopathy) and risk of bias was assessed using a validated Cochrane Checklist adjusted for this purpose. Additionally, an overview of results of articles published in 21 meta-analyses was added, considering a group of myelopathy with or without radiculopathy.

Results

Seven articles that compared intervertebral devices in patients with radiculopathy (excluding patients with myelopathy) were included in the study. Another 31 articles were studied as a mixed group including patients with myelopathy and radiculopathy. Apart from three studies with low risk of bias, all other articles showed intermediate or high risk of bias. Heterotopic ossification was reported to be present in circa 10% of patients, seemingly predominant in patients with radiculopathy, with a very low level of evidence. Radiological signs of adjacent segment degeneration were present at baseline in 50% of patients, and there is low level of evidence that this increased more (10-20%) in the fusion group at long-term follow-up. However, this was only studied in the mixed study population, which is degenerative by diagnosis.

Conclusions

Although the cervical disc prosthesis was introduced to decrease adjacent segment degeneration, convincing radiological evidence for this benefit is lacking. Heterotopic ossification as a complicating factor in the preservation of motion of the device is insufficiently studied. Regarding purely radiological outcomes, currently, no firm conclusion can be drawn for implanting cervical prosthesis versus performing fusion.

INTRODUCTION

Radiculopathy caused by symptomatic cervical disc degenerative disease is a common diagnosis in spine surgery. Usually, cervical radiculopathy is treated by medical interventional methods. If patients are unresponsive to conservative measures, surgical intervention may be considered. Anterior cervical discectomy and fusion (ACDF) has been a common surgical treatment for cervical radiculopathy since it was initially described in the 1950s[1] and became the gold standard procedure in current surgery. Some clinical researchers have demonstrated excellent clinical outcome with low complication rates in long-term follow-up[2-4]. The procedure remained largely unchanged until the 1990s when the use of cages and allograft bone and the addition of anterior cervical locking plates became popular, thereby decreasing iliac crest harvesting complications and minimizing the occurrence of pseudoarthrosis[5-7].

In the last two decades, anterior cervical discectomy with arthroplasty (ACDA), as an alternative procedure to ACDF, gained increasing popularity in the surgical treatment of cervical herniated discs. ACDA is designed to replace the disc with a device that mimics a natural disc by restoring height and maintaining segmental motion. Maintaining the segment mobile has the theoretical advantage that adjacent segment degeneration (ASD) is less in comparison with a device that induces fusion, which may consequently lead to less neck pain and disability. Opponents of this theory claim that degeneration of the cervical spine is a natural process, that will continue to occur, irrespective of patients being subjected to fusion or to a mobile disc device[8].

Quite a number of papers have been published on comparing ACDF with ACDA in the past 10-15 years. Even some reviews and meta-analyses have been published[9]. To the authors' knowledge, there are no studies or reviews yet specifically discussing the radiological findings. The aim of the present study was therefore to present an overview of the currently available literature on the comparison of radiological findings between ACDF with ACDA.

METHODS

The systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement[10].

Search strategy and study selection

Up to August 2016, the electronic databases PubMed, Embase, Web of Science, Cochrane, CENTRAL, and CINAHL were searched using the search strategies as shown in Figure 1. To maintain inter-rater reliability, two of the authors (XY and TJ) independently evaluated the articles by title, abstract or by full article, when necessary, to select the studies that met the predefined selection criteria. Selection criteria were stated as follows:

- the article was published in English or Dutch;
- the study included patients diagnosed with cervical radiculopathy due to disc degeneration disease;
- the study included patients who underwent one-level anterior discectomy, comparing ACDF to ACDA;
- the study reported the radiological outcome with a follow-up period of at least one year;
- the study reported a minimum of 20 patients in each group; and
- the article was published in a peer-reviewed journal;

Performed 2016.08.02
("Cervical Vertebrae"[mesh] OR "Cervic"[tw] OR "cervical"[tw] OR "neck"[mesh] OR "neck"[tw]) AND ("Intervertebral Disc Displacement"[mesh] OR "Slipped disk"[tw] OR "Slipped disks"[tw] OR "Slipped disc"[tw] OR "Slipped discs"[tw] OR "Prolapsed disk"[tw] OR "Prolapsed disks"[tw] OR "Prolapsed disc"[tw] OR "Prolapsed discs"[tw] OR "Herniated disk"[tw] OR "Herniated disks"[tw] OR "Herniated disc"[tw] OR "Herniated discs"[tw] OR "hernia"[tw] OR "Disc Displacement"[tw] OR "Disc Displacements"[tw] OR "Disk Displacement"[tw] OR "Disk Displacements"[tw]] OR "displaced disk"[tw] OR "displaced disks"[tw] OR "displaced disc"[tw] OR "displaced discs"[tw] OR "Radiculopathy"[Mesh] OR "Radiculopathies"[tw] OR "Radiculopathy, Cervical"[tw] OR "Cervical Radiculopathies"[tw] OR "Cervical Radiculopathy"[tw] OR "Radiculopathies, Cervical"[tw] OR "Radicular pain"[tw])
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AND
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AND
(randomized controlled trial OR controlled clinical trial OR randomized controlled trials OR random allocation OR double-blind method OR single-blind method OR clinical trial OR clinical trials OR "clinical trial" OR ((singl* OR doubl* OR trebl* OR tripl*) AND (mask* OR blind*)) OR "latin square" OR placebos OR placebo* OR random* OR "Research Design"[MeSH:noexp] OR comparative study OR evaluation studies OR follow-up studies OR prospective studies OR cross-over studies OR control* OR controlled* OR prospective* OR volunteer* OR randomised controlled trial OR randomised controlled trials OR randomized active control trials OR randomized active control trial OR randomised active control trials OR randomised active control trial OR "RaCT" OR "RaCTs" OR RCT OR RCTs OR control*[tw] OR "latin square" [tw] OR cross-over studies [mh] OR control[tw] OR "Evaluation Studies "[Publication Type] OR "Evaluation Studies as Topic"[Mesh] OR "Pragmatic Clinical Trial" OR "Pragmatic Clinical Trials")

Figure 1 Search strategy

The exclusion criterion included studies in which myelopathy was the primary complaint of the patients.

Any discrepancy in selection between the two reviewers was resolved in open discussion, and if needed, a third reviewer (CVL) could be asked to act as a referee. For study selection, a third reviewer was needed to be a referee two times. For quality appraisal, 11 items were assessed for each paper. Among seven radiculopathy articles, a third reviewer was needed 11

times. For 31 mixed-group studies, a referee was needed 43 times. For the procedure of data extraction, a third reviewer was needed as a referee three times. Reference screening and citation tracking were performed on the identified articles.

Bartels et al.[9] published a study in 2017, concerning 21 meta-analyses that focused on the outcomes of one-level or two-level arthroplasty. It appeared that those meta-analyses included predominantly studies that allowed inclusion of patients suffering from cervical myelopathy. For reasons of completeness, the studies described in the meta-analyses were evaluated additionally.

Quality assessment

The methodological quality of all studies (including those from the mixed population) was assessed by two independent reviewers (XY, TJ), using an adjusted version of the checklist for cohort studies of the Dutch Cochrane Centre[11]. When there was no consensus about the assessment, a third reviewer (CVL) was consulted.

The items reviewed in the assessment were the definition of the patient group, for which a maximum of three points could be attributed; outcome bias, for which three points could be attributed; selection bias, with a maximum of one point; and attribution bias, with a maximum of two points. Studies could be awarded a maximum of total of nine points. Studies were then divided into low (seven to nine points), intermediate (five to six points) or high (four or less points) risk of bias group using a method adapted from Furlan[12].

Data extraction

Data from the studies focusing on cervical radiculopathy were extracted by two independent reviewers (XY and TJ) on the study design, the sample size, the sizes of the intervention group and the control group, the mean age, and sex difference. In addition, the type of prosthesis used in the intervention group and the cage used in the control group were assessed. With regard to outcomes, range of motion (ROM), migration, subsidence, implant loosening, fusion rate, heterotopic ossification (HO), and ASD were extracted.

Level of evidence

The quality of evidence for all outcome parameters was evaluated using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach (according to Atkins et al.[13] and adapted from Furlan et al.[12]).

RESULTS

Characteristics of studies

A total of 603 articles were identified, of which 357 original articles were left after removing duplicates. Titles and abstracts were screened, resulting in 42 eligible articles. These articles were read full text, and in total, 14 studies met all criteria to compare cervical disc prosthesis with fusion.

One study was additionally excluded after meticulously investigating the literature. The article of Burkus et al.[14] had to be excluded because it also contained patients suffering from myelopathy. In Burkus et al.'s study, the seven-year results of a study comparing ACDF with prosthesis were reported, describing seemingly a population consisting of patients with radiculopathy. However, we found another paper of this research group, describing the same population, but with two years' follow-up. From that particular article, it was clear that the population was a mixed one, namely, also patients with myelopathy were included. Therefore, this article (with the seven-year follow-up) was excluded.

Thereafter, five more studies were excluded from the review because they concerned the same RCT. Six studies concerning the same RCT comparing ProDisc-C with ACDF (autograft bone and plate) differed in follow up (two on two years' follow-up, one on four years, one on five years, and another two on seven years' post randomization)[15-20]. We decided to include only the article describing the seven-year results (the longest follow-up). It appeared furthermore that one of the studies describing the seven-year follow-up results of this RCT (Loumeau et al.[18]) described the results of only a part of this group of patients (44 patients) plus seven patients who were enrolled in the continued access arm of the study. However, the results of Loumeau et al.[18] are interesting to us, because they concerned not only the clinical but also, in particular, the radiological outcomes and described the occurrence of HO in detail. It is not clear why HO is not described in detail in the group as a whole in the article of Janssen et al.[15]. Likewise, the article of Auerbach et al.[19] is of interest to us, particularly because the ROM of the whole cervical spine in the group of patients who had a complete set of radiological follow-up after two years. Again, it is not clear why this result is not described in the Murrey et al.[16] article. Delamarter et al.[20] reported additionally the results of 136 continued access patients with two-year follow-up.

Additionally one more study was excluded because it described the one-year follow-up results[21], whereas the three-year follow-up study[22] was also available (ProDisc vs ACDF; polyetheretherketone [PEEK] cage). There was one retrospective study (Mobi-C vs PEEK cage)[23] and one prospective non-RCT that compared different prostheses (Prestige ST, Bryan, ProDisc-C)[24] with ACDF (PEEK cage). The remaining three articles described ACDF methods with autograft or plate[25-27] (Figure 2).

Study characteristics are demonstrated in Table 1. The sample size varied from 49 to 209, with a mean follow-up of 4.6 years after surgery.

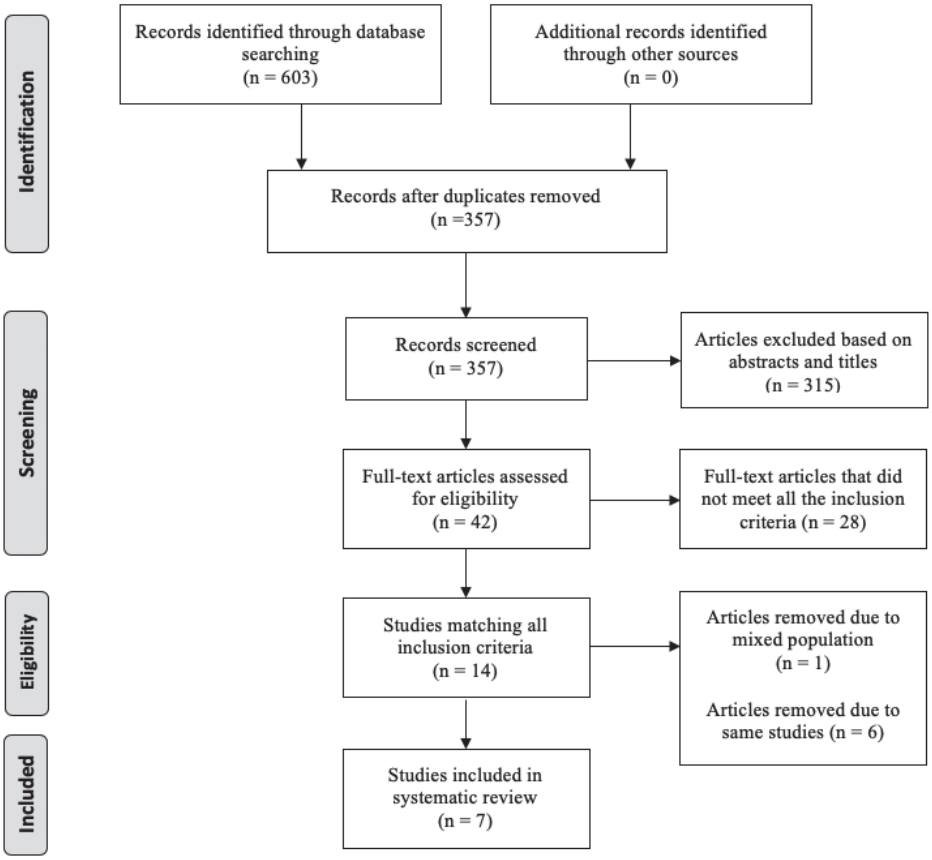

Figure 2 Flow diagram-Studies describing exclusively cervical radiculopathy

Meta-analyses being published already

Twenty-one meta-analyses were identified through the study of Bartels et al.[9]. By means of citation tracking, 206 articles were found on this topic, of which 46 original articles were left after removing duplicates. These articles were read full text and 39 studies were included as they reported radiological outcome on comparison of ACDA and ACDF. Eight of 39 articles concerned same studies; therefore, articles with a longest follow-up were included. In the end, an overview of results of 31 articles was added, considering a group of patients with myelopathy or without radiculopathy (Figure 3). Study characteristics are demonstrated in Table 2.

Table 1 Characteristics of studies describing exclusively cervical radiculopathy

Study (year of publication)	Study design	Prosthetic device	Number of participants		Age (mean ± SD)		Men in %		Follow–up (years)
			ACDA	ACDF	ACDA	ACDF	ACDA	ACDF	
Coric (2013)	Prospective	Bryan, Kineflex	41	43	49.5	49.3	39	42.4	6
Hou (2016)	RCT	Mobi-C	56	51	46.3±7.8	48.5±8.3	58.8	58.3	5
Janssen (2015)	RCT	ProDisc-C	103	106	42.1±8.42	43.5±7.15	45	46	7
Nabhan (2007)	RCT	ProDisc-C	25	24	44#		56.1#		3
Park (2008)	Retrospective	Mobi-C	21	32	45	47	52.4	62.5	20-22 months
Sala (2015)	Prospective non-RCT	Prestige ST, Bryan or Prodisc-C	28	27	41	41	25	33.3	2
Zhang (2014)	RCT	Mobi-C	55	56	44.8	46.7	45.5	46.4	4
Mean			47	48	44.6	45.7	46.0	49.3	4.6

SD: Standard deviation
ACDA: Anterior cervical discectomy with arthroplasty
ACDF: Anterior cervical discectomy and fusion
RCT: Randomly controlled trail
NA: Not available
#: The value of total participants.

Table 2 Characteristics of studies describing myelopathy and cervical radiculopathy

Study (year of publication)	Intervention	Follow-up (years)	Number of participants		Age (mean ± SD)	
			ACDA	ACDF	ACDA	ACDF
Anakwenze (2009)	Prodisc-C	2	89	91	42.2±7.5	41.7±7.9
Burkus (2014)	Prestige ST	7	276#	265#	43.3	43.9
Cheng (2011)	Bryan	3	41	42	47.2±5.7	47.7±5.8
Coric (2006)	Bryan	1.5	17	16	43	43
Coric (2010)	Bryan, Kineflex|C, Discover	2	57	41	46.6	46.3
Coric (2011)	Kinefles|C	2	136	133	43.7±7.76	43.9±7.39
Davis (2015)	Mobi-C	4	225	105	45.3±8.1	46.2±8
Ding (2012)	Prestige LP	1	44	40	46.2±12.3	45.3±11.7
Fay (2014)	Bryan	3	37	40	52.1±9.1	63.0±10.6
Garrido (2010)	Bryan	4	21	26#	40	43.3
Gornet (2016)	Prestige	7	280	265	44.5±8.8	43.9±8.8
Grasso (2015)	Mobi-C or Prodisc-C	2	20	20	47.3	40.5
Hisey (2016)	Mobi-C	5	164	81#	NA	NA
Hou (2014)	Discover	2	149	196	45.8	46.9
Jawahar (2010)	Kineflex-C; Mobi-C; Advent	3	34	59	NA	NA
Kelly (2011)	ProDisc-C	2	100	99	42.1±8.4	43.5±7.1
Kim (2009)	Bryan	1.5	51	54	45.3	50.5
Li (2014)	DCI	2	39#	42#	45.3±8.6	49.5±9.3
Plillips (2015)	PCM	5	218#	185#	45.3±9.0	43.7±8.3
Porchet (2004)	Prestige II	2	27	28	443±8.9	43±6.9
Riina (2008)	Prestige ST	2	10	9	40.8±8.8	38.1±4.9
Robertson (2005)	Bryan	2	74	158	45.7	45.5
Rozankovic (2016)	Discover	2	51	50	41.32±8.8	41.94±9.36
Sasso (2007)	Bryan	2	56#	59#	42.5±7.8	46.1±7.8
Sasso (2011)	Bryan	4	242	221#	NA	NA
Sun (2008)	NA	1	NA	NA	42	
Sun (2012)	Bryan	5	26	24	44.0±6.9	47.5±5.1
Vaccaro (2013)	SECURE-C	2	240	140	43.4 ± 7.50	44.4 ± 7.86
Wang (2008)	Bryan	2	28	31	42	43
Yan (2017)	Bryan	8	39#	54#	48.83±6.70	48.72±7.33
Zhang (2012)	Bryan	2	60	60	44.77±5.60	45.57±5.83

SD: Standard deviation
ACDA: Anterior cervical discectomy with arthroplasty
ACDF: Anterior cervical discectomy and fusion
NA: Not available
#: Follow-up rate less than 80%

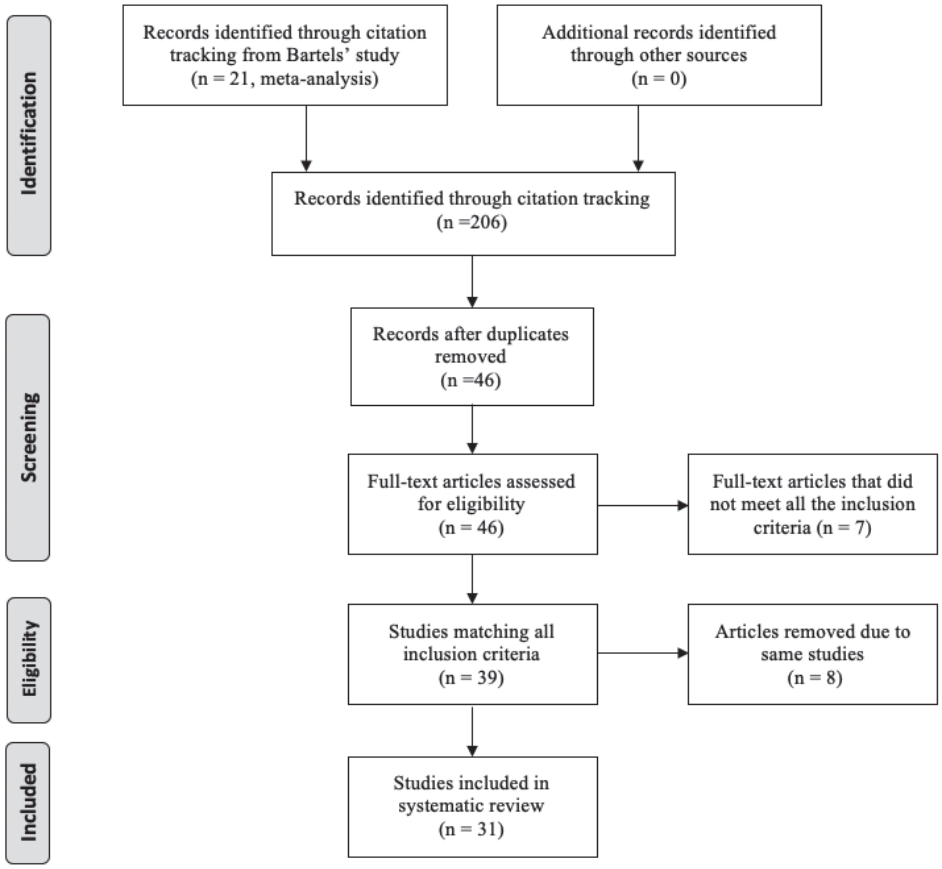

Figure 3 Flow diagram-Studies describing myelopathy and cervical radiculopathy

Quality assessment in radiculopathy studies

None of the studies showed low risk of bias. Three articles[15,25,27] scored five points, indicating intermediate risk of bias. One article[24] scored four points and the other three articles[22,23,26] scored three points, indicating high risk of bias (Table 3).

Quality assessment in mixed studies

Subsequently, risk of bias analysis was performed for the 31 studies on the mixed population (Table 4). Likewise, a maximum of nine points was to be awarded. There were three studies[28-30] with low risk of bias, seven studies with intermediate risk of bias, and 21 studies had high risk of bias.

Table 3 Risk of bias analysis of studies describing exclusively cervical radiculopathy

Study (year of publication)	Total risk of bias score (9)	Patient group and study goal (3)	Outcome properly examined (3)	Absence of selection bias (1)	Absence of attribution bias (2)
Coric (2013)	5*	**	*	-	**
Hou (2016)	5*	**	*	*	*
Janssen (2015)	5*	**	*	*	*
Nabhan (2007)	3*	*	-	*	*
Park (2008)	3*	**	*	-	-
Sala (2015)	4*	**	-	*	*
Zhang (2014)	3*	**	*	-	-

Table 4 Risk of bias analysis of studies describing myelopathy and cervical radiculopathy.

Study (year of publication)	Total risk of bias score (9)	Patient group and study goal (3)	Outcome properly examined (3)	Absence of selection bias (1)	Absence of attribution bias (2)
Anakwenze (2009)	4*	***	-	-	*
Burkus (2014)	4*	***	*	-	-
Cheng (2011)	5*	**	**	*	-
Coric (2006)	4*	**	*	-	*
Coric (2010)	3*	**	*	-	-
Coric (2011)	4*	***	*	-	-
Davis (2015)	7*	***	***	-	*
Ding (2012)	4*	**	*	-	*
Fay (2014)	7*	***	**	*	*
Garrido (2010)	2*	**	-	-	-
Gornet (2016)	4*	***	*	-	-
Grasso (2015)	5*	***	*	-	*
Hisey (2016)	4*	**	*	-	*
Hou (2014)	7*	***	**	-	**
Jawahar (2014)	5*	**	*	*	*
Kelly (2011)	4*	***	-	-	*
Kim (2009)	5*	**	**	-	*
Li (2014)	6*	**	**	-	**
Phillips (2015)	4*	***	*	-	-
Porchet (2004)	6*	***	*	*	*
Riina (2008)	4*	**	*	-	*
Robertson (2005)	4*	***	*	-	-
Rozankovic (2016)	4*	**	*	*	-
Sasso (2007)	3*	**	*	-	-
Sasso (2011)	2*	**	-	-	-
Sun (2008)	2*	-	*	-	*
Sun (2012)	4*	**	*	-	*
Vaccaro (2013)	4*	***	-	-	*
Wang (2008)	4*	**	*	-	*
Yan (2017)	3*	**	*	-	-
Zhang (2012)	5*	***	**	-	-

Range of motion

Definition of range of motion

Two methods to determine the ROM were described: one method described the degrees change in angle measured as a Cobb angle per segment being defined as 'the difference in treated segment angle between full flexion and extension in lateral radiographs'[23,25,26]. Other studies obtained total cervical ROM from flexion and extension radiographs[19,24,27]. The majority of studies failed to give a definition of range of motion[15-18,24].

ROM in studies describing patients with exclusively cervical radiculopathy

Five[15,23,25-27] of seven studies gave data for ROM on the level of the prosthesis, one study[24] reported on ROM of the whole cervical spine and one study[22] did not mention data concerning ROM (Table 5). The average ROM at the index level for ACDA was 9.0 degrees with a range of 5.4 to 15.2 degrees[15,23,25-27]. In four of seven studies, the average ROM for the ACDF group was also measured, and this resulted in an average motion of 0.4 degrees[15,25-27].

Sala et al.[24] reported on the ROM of the whole cervical spine and demonstrated similar cervical ROM in both ACDF and ACDA groups at two years' follow-up. Although Janssen et al.[15] does not describe ROM in the whole cervical spine, Auerbach et al., describing the same patient population at two years' follow-up, additionally give results of the ROM of the whole cervical spine and report in the ACDA group an increase of 5.9 degrees of motion in comparison to baseline motion, whereas a decrease of 0.8 degrees of motion in the ACDF group is reported[19]. However, this is focussing on the change in relation to baseline data.

ROM in studies describing patients with myelopathy and cervical radiculopathy

Twenty-four of 31 studies reported data on ROM after anterior discectomy (Table 6). The average ROM in the ACDA group was 9.4 degrees (range 5.2 to 23.5 degrees). The ROM for ACDF was 0.94 degrees on average (range 0 to 1.8 degrees). Coric et al.[31] did not report on a value for the ROM but reported the change in ROM at the index level instead: in the ACDA group, angular motion was improved by 0.91 degrees and reduced by 7.8 degrees in the ACDF group. Instead of ROM at the index level, Davis et al.[29] reported ROM of the superior and inferior levels of the index level, which were 10.0 ± 6.0 degrees and 8.2 ± 5.3 degrees, respectively, in the ACDA group. The ROM in the ACDF group was not provided.

Wang et al.[32] reported a ROM of the whole cervical spine, ranging from C3 to C7, and reported a ROM of 27.6 degrees in the ACDA group, compared to 26.9 degrees in the ACDF group (not statistically different). Similarly, Grasso[33] reported the ROM of the whole cervical spine to be 47.2 (± 6.6) degrees in the ACDA group and 36.5 (± 7.3) degrees in the ACDF group (no statistical information). Likewise, Li et al.[34] and Yan et al.[35] not only reported segmental ROM but also described ROM of the whole cervical spine. Li et al.[34] reported 47.5 (± 19.8) degrees in ACDA group and 35.8 (± 17.6) degrees in ACDF group (statistically different). Yan et al.[35] reported a ROM of 42.8

Table 5 Radiological outcomes of studies describing exclusively cervical radiculopathy

Study (year of publication)	Range of motion		Migration		Subsidence		Implant loosening		Fusion rate	Pseudarthrosis	HO	Bridging bone
	ACDA	ACDF	ACDA	ACDF	ACDA	ACDF	ACDA	ACDF	ACDF	ACDF	ACDA	ACDA
Coric (2013)	8.6°	0.2°	0	0	0	NA	0	1(3%)	97%	NA	NA	7(17%)
Hou (2016)	5.4±0.9°	0.4±0.3°	NA	NA	NA	NA	NA	NA	NA	NA	0	NA
Janssen (2015)	8.12±5.91°	0.66±0.58°	NA	NA	NA	NA	NA	NA	NA	NA	NA	8(11%)
Nabhan (2007)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Park (2008)	15.2°	NA	NA	NA	0	5(15.6%)	NA	NA	NA	NA	0	NA
Sala (2015)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Zhang (2014)	7.9°†	0.2°†	3(5.4%)	NA	0	0	NA	NA	NA	1(1.8%)	18(32.7%) *	NA
Mean	9.0	0.4	-	-	-	-	-	-	-	-	-	-

ACDA: Anterior cervical discectomy with arthroplasty
ACDF: Anterior cervical discectomy and fusion
HO: Heterotopic ossification
NA: Not available
†: The value is estimated from the graph in the study
*: McAfee grading system

Table 6 Radiological outcomes of studies describing myelopathy and cervical radiculopathy

Study (year of publication)	Range of motion		Migration		Subsidence		Implant loosening		Fusion rate	Pseudarthrosis	HO	Bridging bone
	ACDA	ACDF	ACDA	ACDF	ACDA	ACDF	ACDA	ACDF	ACDF	ACDF	ACDA	ACDA
Anakwenze (2009)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Burkus (2014)	6.75°	0.48°	1	0	7 (4.2%)	4 (3.1%)	6 (3.1%)	7 (3.1%)	96.9%	NA	NA	20(10%)
Cheng (2011)	7.4° ± 0.5°	0.6° ± 0.2°	NA	NA	0	NA	0	NA	90.5%	3(7.1%)	1(2.4%)	NA
Coric (2006)	7°	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	0
Coric (2010)	+0.91°*	-7.8°*	NA	NA	NA	NA	0	0	97%	NA	3(5.6%)	NA
Coric (2011)	9.8°	0.8°	2	NA	1	NA	NA	0	82%	3(2.6%)	1(1%)	NA
Davis (2015)	S=10.0°±6° I=8.2°±5.3°	NA	1	0	0	0	NA	NA	92.2%%	NA	25.6% (G3+G4)†	NA
Ding (2012)	13.5°	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Fay (2014)	23.5° ±7.8°	1.6°±1°	NA	NA	NA	NA	NA	NA	100%	0	NA	NA
Garrido (2010)	NA	NA	NA	NA	NA	NA	NA	NA	NA	1(3.8%)	NA	NA
Gornet (2016)	6.78°	NA	NA	NA	NA	NA	NA	NA	96%	NA	44(15.7%)	36(13%)
Grasso (2015)	47.2°±6.6°§	36.5°±7.3°§	NA	NA	0	0	0	0	NA	NA	0	NA
Hisey (2016)	10°	<1°	0	0	NA	NA	NA	NA	NA	5	8.5%-G4†	NA
Hou (2014)	Single: 11.6° ±1.1° Double: 11.0° ±1.9°	Single: 2.0° ±0.8° Double: 1.7° ±0.2°	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Jawahar (2010)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Kelly (2011)	9.5°	0.9°	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

Table 6 Radiological outcomes of studies describing myelopathy and cervical radiculopathy (continued)

Study (year of publication)	Range of motion		Migration		Subsidence		Implant loosening		Fusion rate	Pseudarthrosis	HO	Bridging bone
	ACDA	ACDF	ACDA	ACDF	ACDA	ACDF	ACDA	ACDF	ACDF	ACDF	ACDA	ACDA
Kim (2009)	Single: 12.1° ±2° Double: 12.3° ±1.9°	Single: 2.3° ±0.8° Double: 1.3° ±0.2°	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Li (2014)	8.9°±4.4°/ 47.5°±19.8°§	0.8°±0.7° 35.8°±17.6°§	1	NA	2	2	NA	NA	94.9%	2	0	NA
Phillips (2015)	5.2°±3.8°	0.5°±0.5°	NA	NA	NA	NA	NA	NA	94.4% (119/126)	NA	6.7%-G3† (10/149) 6.0%-G4† (9/149)	NA
Porchet (2004)	5.9°	1.1°	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Riina (2008)	NA	NA	NA	NA	NA	NA	0	NA	9(100%)	NA	NA	0
Rozankovic (2016)	NA	NA	0	1	NA	NA	NA	NA	98%	1	4	NA
Robertson (2005)	NA	NA	NA	NA	NA	NA	NA	NA	NA	13	NA	NA
Sasso (2007)	7.04° ± 4.29°	0.85° ± 0.71°	NA	NA	NA	NA	0	NA	NA	NA	0	NA
Sasso (2011)	8.5°	1.1°	NA	NA	NA	NA	0	NA	NA	NA	NA	NA
Sun (2008)	11.2° ± 3.9°¶	14.4° ± 4.9°¶	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Sun (2012)	NA	NA	NA	NA	NA	NA	NA	NA	100%	NA	11(42.3%): 1-G2†; 8-G3†; 2-G4†	NA
Vaccaro (2013)	9.7°	NA	0	NA	0	NA	0	NA	89.1%	NA	NA	NA
Wang (2008)	27.6° ± 4.7°§	26.9° ± 0.6°§	NA	NA	NA	NA	NA	NA	NA	NA	2	NA

Table 6 Radiological outcomes of studies describing myelopathy and cervical radiculopathy (continued)

Study (year of publication)	Range of motion		Migration		Subsidence		Implant loosening		Fusion rate	Pseudarthrosis	HO	Bridging bone
	ACDA	ACDF	ACDA	ACDF	ACDA	ACDF	ACDA	ACDF	ACDF	ACDF	ACDA	ACDA
Yan (2017)	6.60°±4.1°/ 42.8°±6.9°§	0/ 39.6°±6.5°§	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Zhang (2012)	8.79° ± 0.89°	0.79° ± 0.63°	0	0	0	0	NA	NA	NA	NA	7(12.5%): 3-G1†; 3-G2†; 1-G3†	NA

ACDA: Anterior cervical discectomy with arthroplasty
ACDF: Anterior cervical discectomy and fusion
HO: Heterotopic ossification
NA: Not available
S: Superior level
I: Inferior level
Single: patient group of single level surgery
Double: patient group of double level surgery
*: The degree of angular motion improved
§: Range of motion of global cervical spine
†: McAfee grading system
¶: Range of motion of the adjacent space

degrees from C2 to C7 in the ACDA group and a ROM of 39.6 degrees in the ACDF group (not statistically different).

Level of evidence

The level of evidence for ROM at the index level is only lowered with one level because most of articles have a high or intermediate risk of bias. Therefore, the level of evidence that the segment in which the prosthesis was implanted stays mobile is moderate (considering that a mean value is given, and no data on percentages of patients were given).

The level of evidence for ROM of the whole cervical spine is lowered with three levels. All articles have a high or intermediate risk of bias, findings are inconsistent, and estimates of effect are not sufficiently precise as not all articles state the exact data or statistically significant difference. Therefore, the level of evidence that the ROM of the whole cervical spine is comparable in ACDA and ACDF is very low.

In conclusion, motion at the index level in the ACDA group remained present and disappeared in the ACDF group. The average ROM in the ACDA group is equivalent in patients suffering from exclusively cervical radiculopathy (9.0) in comparison with the mixed population group (9.3). The results on ROM of the whole cervical spine are inconclusive.

Migration

Definition of migration

To grade migration of the implant material, the definition 'more than a 3-mm anteroposterior slip of the implant parallel to the vertebral endplates'[17,18] was used, if any definition was used at all.

Migration in studies describing patients with exclusively cervical radiculopathy

Three of seven studies provided data of disc implant migration (Table 5). Zhang et al.[26] reported that in three patients (5.4%), the prosthesis moved anteriorly over a distance of 2-3 mm without any relevant clinical symptoms. In another two studies[17,27], no migration was detected in ACDA. Coric et al.[27] also reported that no migration of the implanted cage was found.

Migration in studies describing patients with myelopathy and cervical radiculopathy

Eight of 31 studies reported results regarding migration of the device (Table 6). Coric et al.[36] reported only two cases (1.5%) in which the prosthesis migrated. Davis et al.[29], Li et al.[34], and Burkus et al.[14], respectively, reported one case of migration (0.4%, 2.6%, and 0.4%). Rozankovic et al.[37], Zhang et al.[38], Hisey et al.[39], and Vaccaro et al.[40] did not observe migration of a prosthesis. Migration of a cage in ACDF was observed in only one patient in the whole group of studies[37].

Table 7 Adjacent segment degeneration

Study (year of publication)	Adjacent segment degeneration (patients)			Baseline data at adjacent level
	ACDA: N. (rate)	ACDF: N. (rate)	Difference with significance (P-value)	
Studies describing myelopathy and cervical radiculopathy				
Anakwenze (2009)	NA	NA	-	-
Burkus (2014)	11(4.6%)	24(11.9%)	Yes (0.008)	No
Cheng (2011)	NA	NA	-	-
Coric (2006)	NA	NA	-	-
Coric (2010)	1 (2.5%)	3 (8.1%)	NA	No
Coric (2011)	62%	82%	NA	Yes
Davis (2015)	S:27.6% I: 16.4%	S: 64.7% I: 56.2%	Yes (P<0.0001) Yes (P<0.0001)	Yes
Ding (2012)	NA	NA	-	-
Fay (2014)	NA	NA	-	-
Garrido (2010)	1(5.6%)	3(15%)	NA	No
Gornet (2016)	NA	NA	-	-
Grasso (2015)	NA	NA	-	-
Hisey (2016)	S: 38% I: 37%	S: 55% I: 56%	S: Yes (<0.05) I: Yes (<0.05)	Yes
Hou (2014)	NA	NA	-	-
Jawahar (2010)	18%	15%	No (P=0.885)	No
Kelly (2011)	NA	NA	-	-
Kim (2009)	NA	NA	-	No
Li (2014)	12.8% (5/39)	14.3% (6/42)	No (NA)	No
Phillips (2015)	S: 33.1% I: 49.2%	S: 50.9% I: 51.7%	S: Yes (0.006) I: No (0.779)	Yes
Porchet (2004)	NA	NA	-	No
Riina (2008)	NA	NA	-	No
Robertson (2005	13(17.5%) *	54(34.6%) *	0.009	Yes
Rozankovic (2016)	NA	NA	-	No
Sasso (2007)	3(5.4%)	2(3.4%)	NA	No
Sasso (2011)	10 (4.1%)	9 (4.1%)	No (1.000)	No
Sun (2008)	NA	NA	-	-
Sun (2012)	9 segments	29 segments	P<0.001	Yes
Vaccaro (2013)	4 (1.7%)	2 (1.4%)	NA	No
Wang (2008)	NA	1(3.2%)	-	No
Yan (2017)	13(44.83%)	19(48.72%)	No (NA)	No
Zhang (2012)	1(1.7%)	3(5%)	NA	No
Studies describing patients with exclusively cervical radiculopathy				
Coric (2013)	2 (4.9%)	1 (3.0%)	No (NA)	No
Hou (2016)	1(2.0%)	NA	-	No
Janssen (2015)	6(6%)	13(12.6%)	NA	No

Table 7 Adjacent segment degeneration (continued)

Study (year of publication)	Adjacent segment degeneration (patients)			Baseline data at adjacent level
	ACDA: N. (rate)	ACDF: N. (rate)	Difference with significance (P-value)	
Nabhan (2007)	NA	1	-	No
Park (2008)	NA	NA	-	-
Sala (2015)	NA	NA	-	-
Zhang (2014)	NA	4(7.1%)	-	No

ACDA: Anterior cervical discectomy with arthroplasty
ACDF: Anterior cervical discectomy and fusion
N: Number of patients
NA: Not available
S: Superior level
I: Inferior level
*: This number include anterior osteophytes (14 in ACDA and 4 in ACDF), degenerative disc degeneration (10 in ACDA and 11 in ACDF) and calcification (5 in ACDA and 5 in ACDF)

Level of evidence

The level of evidence is lowered with three levels. Most of articles have a high or intermediate risk of bias, findings are inconsistent, and estimates of effect are not sufficiently precise as not all articles state the statistically significant difference. Therefore, the level of evidence is very low.

In conclusion, based on the abovementioned data, migration of the device is only a minor issue but occurs more often with prostheses than with cages.

Subsidence

Definition of subsidence

Subsidence was defined as 'bone penetration of the implant more than 3 mm into the superior and/or inferior endplate of the adjacent vertebral body'[17,18].

Subsidence in studies describing patients with exclusively cervical radiculopathy

Zigler et al.[17] found only one (0.5%) case of prosthesis subsidence at five years' follow-up in 209 patients; no subsidence was observed in the ACDF group (Table 5). Park et al.[23] demonstrated that five of 53 patients (15.6%) underwent insertion of a cage, experiencing subsidence. Coric et al.[27] found no subsidence in prosthesis group without providing information of the fusion group. Zhang et al.[26] reported that no patient can be detected with subsidence. The other three articles do not mention subsidence.

Subsidence in studies describing patients with myelopathy and cervical radiculopathy

Burkus et al.[14] found seven cases (4.2%) of subsidence in the ACDA group and four cases (3.1%) in the ACDF group (Table 6). In Li et al.[34], two subjects in both the ACDA (5.1%)

and the ACDF (4.8%) groups were detected to have subsidence. Coric et al.[36] reported one subsidence case in the ACDA group and none in the ACDF group. Cheng et al.[41] and Vaccaro et al.[40] reported that no prosthesis subsided. Zhang et al.[38], Grasso[33], and Davis et al.[29] claimed subsidence can be detected in neither the ACDA nor the ACDF group. The other 23 articles do not mention subsidence.

Level of evidence

The level of evidence is lowered by two levels. Most of articles have a high or intermediate risk of bias, and estimates of effect are not sufficiently precise as most articles lack statistics on this subject. Therefore, the level of evidence that subsidence occurs equally in prosthesis and in cage is low.

Overall, subsidence is reported only in a small percentage of cases.

Implant loosening

Definition of implant loosening

No definition was given to define implant loosening.

Implant loosening in studies describing patients with exclusively cervical radiculopathy

Nabhan et al.[21] evaluated implant loosening in the one-year follow-up result and reported no occurrence of this in the ACDA group. Coric et al.[27] reported one implant loosening case (3%) in ACDF group but none for ACDA group (Table 5).

Implant loosening in studies describing patients with myelopathy and cervical radiculopathy

Six (3.1%) and seven (3.1%) cases of implant loosening were reported in ACDA and ACDF, respectively, by Burkus et al.[14] (Table 6). Additionally, five articles (Cheng et al.[41], Vaccaro et al.[40], Sasso et al.[42], Sasso et al.[43], Riina et al.[44]) reported no implant loosening without mentioning the result of the ACDF group. Coric et al.[36] found no implant loosening in fusion patients but did not provide the data for patients who underwent arthroplasty. Neither prosthesis nor cage loosening was found throughout follow-up, reported by Coric et al.[31] and Grasso[33].

Level of evidence

The level of evidence is lowered with three levels. All articles have a high or intermediate risk of bias, findings are inconsistent, and estimates of effect are not sufficiently precise as not all articles state the statistically significant difference. Therefore, the level of evidence that implant loosening is comparable in prosthesis and cage is very low.

In conclusion, the majority of authors do not report on implant loosening.

Fusion rate

Definition of fusion rate

Several definitions of fusion were used and, logically, were applied only to the ACDF patients and not in the prosthesis patients. Janssen et al.[15] did not report fusion in the seven-year evaluation report. Zigler et al.[17], giving the results of the same population at the five-year evaluation point, was very specific and judged fusion to be present only if all of the following were true: 'more than 50% of trabecular bridging on X-ray', 'no motion (≤2 degrees) on dynamic X-ray, and 'no implant loosening'.

Fusion rate in studies describing patients with exclusively cervical radiculopathy

Zhang et al.[26] reported only one patient with 'pseudarthrosis' in the ACDF group (1.8%) (Table 5). Zigler et al.[17] reported a 92.5% fusion rate in their five-year follow-up, and a fusion rate of 97% was reported by Coric et al.[27].

Fusion rate in studies describing patients with myelopathy and cervical radiculopathy

Thirteen studies reported fusion rate in the ACDF group, which ranged from 82%[36] to 100%[28] (Table 6). Alternatively, pseudarthrosis was reported by Garrido et al.[45] (one case), Hisey et al.[39] (five cases) and Robertson et al.[46] (13 cases). The remaining 15 studies did not study fusion nor pseudarthrosis.

Level of evidence

The level of evidence is lowered with two levels because most of articles have a high or intermediate risk of bias and data are insufficiently precise. Therefore, the level of evidence that fusion is present in ACDF is low.

In conclusion, fusion rates are high in ACDF, namely over 90%, but the level of evidence is low.

Heterotopic ossification

Definition of heterotopic ossification

HO can be classified according to the classification system of McAfee et al.[47]. In this classification system, the amount of bone overgrowing the level of interest in which a prosthesis was placed is quantified from grade 0 (no HO present) to grade IV (complete fusion of the treated segment without movement in flexion and extension).

Heterotopic ossification in studies describing patients with exclusively cervical radiculopathy

Four studies reported on data regarding HO in the prosthesis group (Table 5). Only Loumeau et al.[18] and Zhang et al.[26] used the McAfee classification. In Zhang et al.[26] (four-year follow-up), 18 of 55 patients (32.7%) demonstrated HO (McAfee scoring): 11 patients were classi-

fied as grade I, five patients were classified as Grade II, and two patients were classified as Grade III. These results were reported after one year of follow-up, and it was reported that no increase of HO developed in the subsequent three years. However, it was not specified that all radiographs were evaluated for HO again at four years' follow-up. Loumeau et al.[18] reported HO (McAfee grading) to be present in 90% of patients who were fitted with a prosthesis. Six patients (15%) were classified as Grade I, six patients (15%) were classified as Grade II, 17 patients (44%) were classified as Grade III, and six patients (15%) were classified as Grade IV HO. Janssen et al.[15] and Coric et al.[27] used another nomenclature, namely, 'presence of bridging bone', which can be defined as McAfee Grade IV. At seven-year follow-up, 11% of patients with a prosthesis demonstrated bridging bone reported by Janssen et al.[15] and, in another study, 17% by Coric et al.[27] (six-year follow-up). Park et al.[23] and Hou et al.[25] reported the absence of HO but failed to define or classify it.

Heterotopic ossification in studies describing patients with myelopathy and cervical radiculopathy

The presence of HO (or presence of bridging bone) was reported in 17 studies (Table 6). Five studies[29,38,39,48,49] evaluated HO by means of the McAfee classification. Zhang et al.[38] (two-year follow-up) reported that three patients (out of 60) had Grade I, three patients had Grade II, and one patient had Grade III. In Phillips et al.[48] (five-year follow-up), ten patients (6.7%) had Grade III and nine patients (6.0%) had Grade IV HO. Hisey et al.[39] reported 8.5% of patients had Grade IV HO. Davis et al.[29] claimed that Grade III or IV HO was observed in 25.6% of 187 ACDA patients at four years' follow-up. In study of Sun et al.[49], which is a retrospective study, 11 patients (42.3%) were found with HO: one was classified as Grade II, eight were classified as Grade III, and two were classified as Grade IV.

Of the three studies reporting on bridging bone, Burkus et al.[14] reported 20 patients (10%) with a bony bridge at the ACDA index level, and both Coric et al.[50] and Riina et al.[44] observed no case of bridging bone in with a prosthesis. The other studies reported the presence of HO but failed to define or classify it.

Level of evidence

The level of evidence is lowered with three levels. Most of articles have a high or intermediate risk of bias, findings are inconsistent, and data are insufficiently precise. Therefore, the level of evidence that HO is present in 11-90% of patients with radiculopathy and in 1-42% in patients of a mixed population is very low.

In conclusion, HO is only reported in a reliable manner (McAfee classification or bridging bone presence) in a minority of studies. In the radiculopathy studies, the occurrence of HO is higher as is the degree of HO, in comparison with the mixed population group.

Adjacent segment degeneration

Definition of adjacent segment degeneration

To properly judge ASD, defined as degeneration at the level adjacent to the target level, the degeneration at baseline (preoperative) on this adjacent level should be known. Only six articles judged ASD by comparing degeneration with the preoperative situation. Coric et al.[36] evaluated ASD by comparing x-rays from the preoperative period to x-rays produced at the end of follow-up (two-year follow-up) and classified it as none, mild, moderate and severe according to previous literature[51]. The other two articles[46,49] reported whether deterioration of degeneration relative to baseline degeneration was present. Phillips et al.[48] used the same method to determine ASD, while Davis et al.[29] and Hisey et al.[39] evaluated ASD by means of the Kellgren-Lawrence grading scale[52]. All other articles failed to describe a proper radiological measurement of ASD, and reported the rate of second surgery at the level directly adjacent to the treated level instead, which will be disregarded in this review.

Studies describing patients with exclusively cervical radiculopathy

None of the studies reported on radiologically evaluated ASD.

Studies describing patients with myelopathy and cervical radiculopathy

As stated earlier, only six studies reported on radiological ASD in a meaningful way, namely, by comparing to baseline data (Table 7). Of the six studies, only Coric et al.[36] provided baseline information of ASD. At two years' follow-up, Coric et al.[36] reported that ASD increased from 52% preoperatively to 62% postoperatively in ACDA, and increased from 59% preoperatively to 82% postoperatively in ACDF, without mentioning statistics. Presumably, this difference was not statistically different. Phillips et al.[48] reported that worsening of degeneration at the superior adjacent disc level in 33.1% in ACDA patients and in 50.9% in ACDF patients (statistically significant), whereas worsening of ASD in the inferior adjacent level was 49.2% in ACDA versus 51.7% in ACDF patients (not significant). Likewise, at the five-year follow-up, Hisey et al.[39] reported worsening of ASD in ACDA in 38% of patients versus worsening of ASD in ACDF in 55% of patients for the superior level, and worsening of ASD in ACDA in 37% of patients versus worsening of ASD in ACDF in 56% of patients for the inferior level (both significantly different). Additionally, Sun et al.[49] reported that nine segments (17.6%) were detected to have ASD in ACDA, whereas 29 segments (60.4%) were detected to have ASD in ACDF (significantly different). Robertson et al.[46] has a similar result, in which 13 patients (17.5%) had ASD in the ACDA group and 54 patients (34.6%) had ASD in the ACDF group (significantly different). Davis et al.[29] reported worsening of ASD in relation to baseline, and reported worsening of ASD to be higher in the fusion group than in the prosthesis group, for both the level superior and inferior to the index level: superior, 27.6% (ACDA) versus 64.7% (ACDF); inferior, 16.4% (ACDA) versus 56.2% (ACDF), both statistically different.

Level of evidence

The level of evidence is lowered with two levels. Most of the articles have a high or intermediate risk of bias, and estimates of effect are not sufficiently described. Therefore, the level of evidence that ASD occurs more often in ACDF than in ACDA is low.

In conclusion, only limited information is present on ASD. At baseline, ASD is already high, as is to be expected in a population with myelopathy caused by degeneration. The increase in ASD tends to be higher in the fusion group, but it seems that this does not lead to statistically significant differences. Unfortunately, no results on ASD are available in a group of patients with only radiculopathy.

DISCUSSION

The rationale of implanting an artificial disc after anterior discectomy is to preserve motion and to avoid ASD, which can lead to clinical symptoms in due time. The focus in comparing the outcome of implanting a prosthesis with the outcome of implanting a conventional cage should logically be on the signs of ASD. This systematic review revealed that only six[29,36,39,46,48,49] out of 38 studies adequately studied ASD radiologically. None of these studies concerned exclusively patients with radiculopathy, and one study[36] reported baseline presence of degeneration at the adjacent level in a substantial number of included patients, namely, 50%. ASD seemed to deteriorate in a higher percentage of patients (ca. 10-20%) in patients who were subjected to fusion surgery. It is therefore reasonable to state that degeneration of the cervical spine in an ongoing process that progresses irrespective of the immobilization of a segment. However, because data are scarce, the level of evidence is low, and research for radiological ASD was only performed in a population that has degeneration by diagnosis, these data are not convincing.

This literature overview demonstrated that ACDA preserved the mobility at the target level in the cervical spine whereas ACDF resulted in solid fusion in the vast majority of patients. However, ROM was reported as a mean value. It would be more interesting if we could get information about the percentage of patients in which motion persisted. The results on HO and bridging of bone around the prosthesis demonstrated that, on average, 10% of patients who were fitted with a prosthesis developed a bony rim around the prosthesis, preventing it from remaining mobile. This is not represented through the mean ROM. It can even lead to confusing outcome data. For instance, results from Loumeau et al.[18] demonstrated that Grade III and Grade IV HOs were present in nearly 60% of patients, but the mean ROM presented is >7 degrees in the prosthesis group. It would have been better to dichotomise the data in a group with persistent and non-persistent mobility. Unfortunately, no study reported their results in this way.

The results on the ROM of the whole cervical spine are interesting. The ROM of the whole cervical spine was evaluated in six[19,24,32-35] of 38 studies (two radiculopathy + four mixed), and three[24,32,35] of those studies did not demonstrate a difference between the ACDA and ACDF patients. Li et al.[34] reported a significant difference with more motion in the ACDA group, but yielded large standard deviations. Only Grasso[33] has a higher total cervical ROM of the ACDA group compared with the ACDF group with a statistical significance. This interesting result points in the direction of a self-correcting action of the cervical spine to go back to its original motion pattern.

HO has been one of the major complications after undergoing cervical ACDA[53,54]. Prostheses are designed with the purpose of preserving motion at the target level after anterior discectomy, and the occurrence of overgrowth of bone deprives the target level of staying mobile. Regarding the evaluation studies, the presence of HO is, however, evaluated scarcely. Only seven of 38 studies evaluated HO by means of McAfee et al.[47], and five reported bridging bone, which can be defined as Grade IV by McAfee classification. The incidence of HO after undergoing ACDA varied largely, from 17.8 to 94.1%[55]. This large variation may be due to the method used to evaluate overgrowth of bone. In the McAfee classification, it is essential that islands of bone be identified to grade HO. This can be difficult to discern on x-ray or computed tomography. Furthermore, the results available tend to indicate that occurrence of HO occurs more often in patients with radiculopathy than in patients with myelopathy. Because the cervical spine of patients with radiculopathy is likely to be less degenerative in comparison with the patients with myelopathy, and thus more mobile, HO may be related to the presence of a certain minimal mobility of the cervical spine. However, it may also be that the differences that exist between the design in the several types of prosthesis, such as biomechanical characteristics and endplate articulation components, cause this variation. Some researchers propose this to be a predisposing factor for HO, together with variations in surgical procedure[56,57]. However, again, numbers are too low to draw firm conclusions.

Overviewing the results on HO that are available, although scarce and of very low evidence, it seems that HO occurs on average in 10% of cases (very rude estimate). That number is too low to correlate the occurrence of HO to clinical condition, taking into account the relatively low number of patients included in the studies. Therefore, we cannot be sure that overgrowth of bone does not lead to compression of the neural structures, although this does not seem likely.

Only a minority of patients were demonstrated to have implant subsidence. This is a much lower incidence than generally reported in the literature. Subsidence rates were demonstrated to vary from 13% to 67% in previous studies evaluating ACDF[58-64]. Risk factors that were associated with subsidence are cervical malalignment, absence of a plate, old age[65], or an increased number of treatment levels[66]. The patients studied in this review were not of old age (Table 1), and only one level was operated on. This may explain the low percentage of subsidence observed.

There were several limitations at the review level pertaining to the possible incomplete retrieval of identified study and reporting bias. Although we made all attempt to performed search strategies to include research relevant to radiological outcomes after ACDF and ACDA from patients with radiculopathy, we were not able to include all, resulting in a possible incompletion of relevant studies. As we only included studies published in English and Dutch (two in Chinese in mixed group), those articles reported in other languages were possible omissions, which is an additional limitation to the incomplete retrieval of the identified study. Focusing on specific outcomes with regard to one-level anterior discectomy serves as a reporting bias limitation of this review. To reduce reporting bias, we included all studies regarding to radiological outcomes, reporting on the majority of relevant radiological parameters in each study.

CONCLUSIONS

Based on the radiological evidence that is present in literature, the proclaimed advantages of implanting a prosthesis cannot be corroborated, because it is clear that ASD cannot be avoided, but solid evidence that ASD occurs less in comparison to ACDF is lacking. Nor can the proclaimed disadvantages be confirmed. HO studies are scarce, but the results that are available indicate an occurrence of circa 10%. In conclusion, radiologically, no firm conclusion can be drawn on implanting a prosthesis in comparison with performing fusion.

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Chapter 3

The Size of Cervical Disc Herniation on MRI Does Not Correlate to Clinical Condition

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Submitted

ABSTRACT

Objective

To investigate the correlation between the size of the disc herniation and the clinical condition. Besides that, it was evaluated whether the size of disc herniation at baseline can predict clinical outcome at two-year follow-up.

Methods

A total of 108 patients who underwent anterior discectomy for a cervical radiculopathy due to a herniated disc were analysed for the size of cervical disc herniation at baseline. The size of the cervical disc herniation was qualitatively evaluated on magnetic resonance imaging (MRI), using a four-point scale which was subsequently dichotomized into mild and severe herniation. Clinical condition was evaluated by means of Neck Disability Index (NDI), 36-Item Short Form Health Survey, Visual Analogue Scoring for neck pain and for arm pain at baseline, and at two years postoperatively. Perceived recovery was assessed at two-year follow-up.

Results

At baseline, 46 patients had a mild herniation, and 62 patients had a severe herniation. At baseline, the patients in the mild herniation group had a comparable NDI (44.6 versus 43.8; P=0.799) and SF-36 (59.2 versus 59.4; P=0.895) to the patients in the severe herniation group. Likewise, disabling arm pain was comparable in the mild and severe herniation group (84% versus 73%; P=0.163), and disabling neck pain was also comparable (71% versus 63%, P=0.491). At two years after surgery, no difference was found in any of the clinical parameters between the two groups.

Conclusions

In patients who suffer from cervical radiculopathy, the size of disc herniation measured on MRI was not correlated with clinical condition at baseline, and neither to clinical outcome after surgical treatment at two-year follow-up.

INTRODUCTION

Cervical radiculopathy is a neurological disorder caused by dysfunction of nerve roots exiting the spinal cord in the cervical spine, with an incidence of 1.79 per 1,000 person-years from 2000 to 2009[1]. It typically describes as arm pain along the path of innervation of the affected roots[2], and frequently, with the setting of neck pain[3]. One of the common cause of cervical radiculopathy is a bulging or herniated disc compressing the corresponding nerve root[4].

Cervical radiculopathy is diagnosed based on anamnestic details and physical examination. Imaging of the cervical spine can reveal whether the radiculopathy is caused by compression of the spinal root, for instance by a herniated disc. Magnetic resonance imaging (MRI), which is considered the imaging procedure of choice for patients in whom cervical disc herniation is suspected, is wildly used in diagnosis and treatment planning for patients with cervical radiculopathy. MRI can provide a non-invasive morphologic evaluation of the cervical spine and intervertebral disc and reveal the evidence of degenerative changes. In addition, the size and contour of disc herniations can be measured and identified on MRI, as can the size and proportions of the spinal canal[5], possibly elucidating the aetiology of the clinically diagnosed cervical radiculopathy However, abnormal MRI findings, like bulging discs and disc degenerative changes are frequently present in the demographic of patients that present with cervical radiculopathy. This results in high rates of false-positive findings in the asymptomatic patient[6,7]. Nakashima et al.[8] reported that nearly 90% of asymptomatic subjects had disc bulging, which is defined as the intervertebral disc protruding posteriorly by more than 1 mm. Therefore, it is relevant to evaluate the relationship between the size and shape of cervical disc herniation to clinical symptoms to better understand its relevance.

The objective of the current study is to investigate the correlation between the size of the cervical disc herniation and clinical symptoms. In addition, the prognostic value of the size of disc herniation on MRI on clinical outcome in patients treated by anterior cervical discectomy for cervical radiculopathy was assessed as well.

METHODS

Study design

A prospective, randomized double-blind multicentre trial among patients with cervical radiculopathy due to single-level disc herniation was conducted (Netherlands Cervical Kinematics: NECK trial). Patients were randomly assigned into three groups: anterior cervical discectomy with arthroplasty (ACDA; activC, Aesculap AG, Tuttlingen, Germany), anterior cervical discectomy with fusion (ACDF; Cage standalone) and anterior cervical discectomy without fusion (ACD). Patients (age 18 - 65 years old) with radicular signs and symptoms in one or both arms for at least eight weeks, in who conservative therapy failed were eligible for

inclusion. All patients were diagnosed with cervical radiculopathy by a neurologist in one of the participating hospitals. If MRI demonstrated a single-level cervical disc herniation with or without osteophyte at one level (C3-C4 to C7-Th1) in accordance with clinical signs and symptoms, patients could be included as surgical candidates for the study by the consulting neurosurgeon. Patients with previous cervical surgery, absence of motion or increased anteroposterior (AP) translation or very narrow (< 3 mm) intervertebral space or severe segmental kyphosis (> 3 degrees) at the index level on static or dynamic x-rays, neck pain only or symptoms and signs of chronic myelopathy were excluded. A randomized design with variable block sizes was used, with allocations stratified according to centre. The design and study protocol were published previously[9].

Standard protocol approvals, registrations, and patient consents

The protocol was approved by the Central Medical Ethics Committee Leiden ('Commissie Medische Ethiek Leiden University Medical Centre', decision letter P08.011) and the board of directors of the Rijnland hospital Leiderdorp, Diaconessenhuis Leiden, Haaglanden Medical Centre and Antoniushove the Hague, including an approval for randomization after anaesthetic induction, in agreement with the Central Ethics Committee Leiden. The protocol was also approved by the 'Medical Ethics Committee Noord-Holland' for the Medical Centre Alkmaar (M08−038). The NECK trial was registered at Dutch Trial Register with study identifying number NTR1289. Informed consent was obtained from the participants.

Clinical outcome measurement

Neck Disability Index (NDI) is a 10-item questionnaire on three different aspects: pain intensity, daily work-related activities and nonwork-related activities. Each item is scored from 0 to 5 and the total score ranges from 0 (best score) to 50 (worst score). This 50-point score was converted to a percentage (50 points=100%). The NDI is a modification of the Oswestry Low Back Pain Index and has been shown to be reliable and valid for patients with cervical pathology[10-12].

The 36-Item Short Form Health Survey is a generic health status questionnaire that can easily be filled out at home. The questionnaire consists of 36 items on physical and social status of the patient divided into subscales. The questions are scored on a scale of 0 (worst health) to 100 (ideal health). This questionnaire has been used frequently and is validated in surgical studies on spinal column pathology[13-15]. The physical component summary (PCS) and mental component summary (MCS) are derived from the SF-36 and are summary scores for respectively the Physical Quality of Life and the Mental Quality of Life. The PCS and MCS range from 0 to 100 with higher scores representing better self-reported health.

The Visual Analogue Scale (VAS) pain measures the experienced pain intensity during the week before visiting the research nurse. Pain was assessed on a horizontal 100 mm scale varying from 0 mm (no pain) to 100 mm (worst pain imaginable). Patients do not see the

results of earlier assessments and score the pain experienced at the visit. Reliability, validity and responsiveness of VAS have been shown previously[16]. Disabling neck pain and arm pain were defined as at least 40 mm since this cut-off value is regularly used when VAS is categorized into favourable and unfavourable outcome[17,18].

Finally, patients were asked to judge their post-operative recovery ('perceived recovery') on a scale varying from 'complete recovery' to 'worse than ever' in 7 steps (7-point Likert scale). This outcome scale has been used in previous studies and is regarded valid and responsive to change[19]. 'Complete recovery' and 'almost complete recovery' are defined as a favourable result, which was used to dichotomize the data.

The improvement of clinical outcome was defined as the difference between baseline to two-year follow-up.

The clinical outcomes were comparable between three surgical treatment arms, which has been reported previously[20]. Therefore, the clinical outcomes of the patients were studied irrespective of surgical methods.

Radiological evaluation

MRI were performed at each study centre using a standardized protocol tailored to a 1.5- or 3-Tesla scanner at baseline. Standard sagittal T1 and T2 and T2 axial images were obtained, using 3-mm contiguous slices in all directions and an in-plane resolution of 1 mm^2 or less. The size of cervical disc herniation was evaluated at the operative level at both the left and right side, using a four-point scale: *normal*, completely normal; *mild*, slight bulging of herniated disc; *moderate*, pro/extrusion less than ¼ of foraminal canal; *severe*, pro/extrusion more than ¼ of foraminal canal (Figure 1). For evaluation, data were dichotomized into 'mild herniation group' for those subjects with the classification *normal* and *mild*, and 'severe herniation group' for the classification *moderate* and *severe*. The MRIs were evaluated by neurosurgeons in participating hospital and then independently confirmed by one senior neurosurgeon (CVL) dedicated to spine surgery.

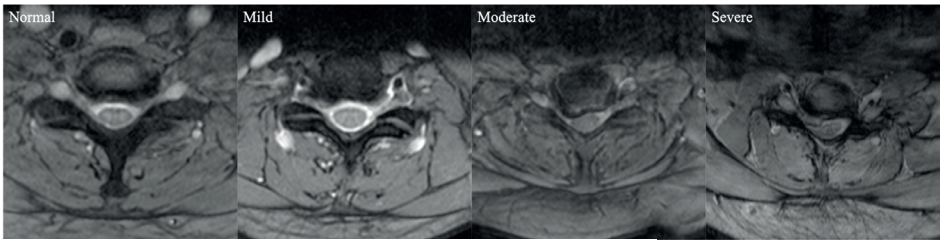

Figure 1 Classification of cervical disc herniation

Statistical analysis

All data were presented as mean ± standard deviation. Student *t*-test was used to compare continuous data and chi-square test for categorical data between groups. Differences between groups at all follow-up points were analysed with repeated measurement analysis. Tests were two tailed, and a P value of < 0.05 was considered significant. SPSS software, version 25.0 was used for all statistical analyses (SPSS, Inc., Chicago, IL, USA).

RESULTS

Demographics

In the NECK trial, 111 patients were included and randomly assigned to ACD (38 patients), ACDF (38 patients) or ACDA (35 patients). At baseline, MRI data were available for 108 patients.

Baseline characteristics are presented in Table 1. The mean age of the study population was 46.8 ± 7.9 years, ranging from 27 to 70 years. There was no difference regarding baseline characteristics between groups.

Table 1 Patient demographics

	Mild group	Severe group	P value
Population	46	62	
Age (years, mean ± SD)	47.1 ± 8.4	46.4 ± 7.8	0.685
BMI (mean ± SD)	26.9 ± 4.1	26.6 ± 4.3	0.714
Man	16 (34.8%)	35 (56.5%)	0.026*
Smoking	17 (38.6%)	27 (43.5%)	0.613
Herniated level			
C5-C6	25	31	
C6-C7	20	31	
C7-Th1	1	0	

SD: Standard deviation
BMI: Body Mass Index

Cervical disc herniation at affected side of operative level

Of 108 patients at baseline, four were classified as *normal*, 42 patients as *mild*, 59 patients as *moderate* and three patients as *severe*. Thus, 46 (43%) patients were included in the 'mild herniation' group and the other 62 (57%) patients were included in 'severe herniation' group.

Correlation of herniation size with clinical outcome

At baseline, the mild herniation group had a comparable NDI value (44.6 ± 15.2 versus 43.8 ± 16.0, P=0.799) and SF-36 (59.2 ± 6.9 versus 59.4 ± 7.7, P=0.895) in comparison to the

severe herniation group. In the mild herniation group, 84% of patients had disabling arm pain, which is similar to the 73% of patients with disabling arm pain in the severe herniation group (P=0.163). For the proportion of patients with disabling neck pain, a comparable result was shown as well (71% versus 63%, P=0.491).

At two years after surgery, the patients in the mild herniation group reported comparable NDI (Figure 2, P=0.091) and SF-36 (Figure 3, P=0.427) values compared to those in the severe herniation group. 17% of patients from the mild herniation group reported disabling arm pain, which is similar to 15% of patients of the severe herniation group (P=0.795). Disabling neck pain was demonstrated in a similar proportion of patients in both groups (22% versus 21%, 0.888). Additionally, 59% of patients in the mild herniation group had a favourable result on perceived recovery which was comparable to 70% of patients in the severe herniation group (P=0.230) (Table 2).

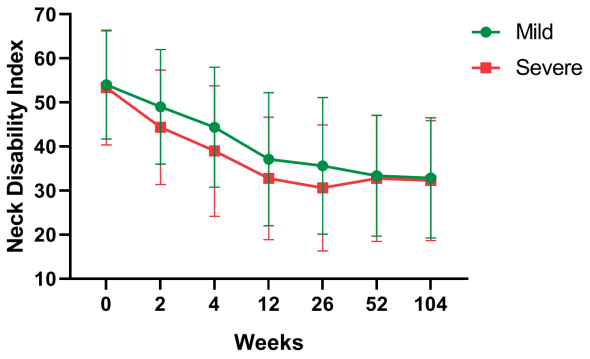

Figure 2 Neck disability index

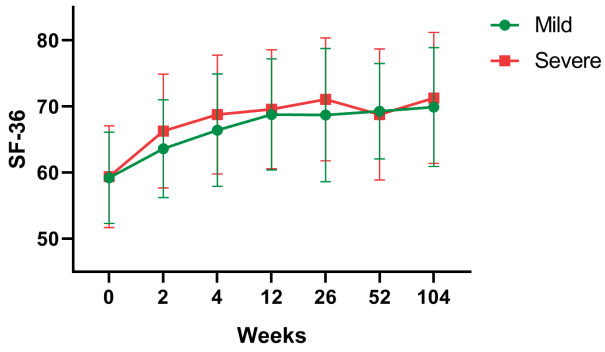

Figure 3 The 36-Item Short Form Health Survey

Table 2 Clinical outcomes

	Baseline			One-year follow-up			Two-year follow-up		
	Normal group	Severe group	P	Normal group	Severe group	P	Normal group	Severe group	P
NDI	44.6 ± 15.2	43.8 ± 16.0	0.799	20.0 ± 16.6	18.9 ± 17.4	0.840	19.1 ± 16.4	18.5 ± 19.6	0.861
SF-36	59.2 ± 6.9	59.4 ± 7.7	0.895	69.3 ± 7.2	68.8 ± 9.9	0.760	69.9 ± 9.0	71.2 ± 9.9	0.495
PCS	41.7 ± 13.5	42.8 ± 15.1	0.690	71.8 ± 22.1	70.7 ± 22.3	0.823	75.0 ± 20.8	71.1 ± 25.8	0.446
MCS	61.5 ± 21.9	55.5 ± 23.2	0.185	77.7 ± 18.3	75.2 ± 22.3	0.553	78.9 ± 17.1	73.9 ± 25.7	0.296
VAS Neck Pain (disabling pain %)	70.5% (31)	62.9% (39)	0.491	22.0% (9)	19.0% (11)	0.716	22.0% (9)	20.8% (11)	0.888
VAS Arm Pain (disabling pain %)	84.1% (37)	72.6% (45)	0.163	14.6% (6)	25.9% (15)	0.178	17.1% (7)	15.1% (8)	0.795
Liker recovery (favourable results %)	-	-	-	63.4% (26)	65.5% (38)	0.829	58.5% (24)	70.4% (38)	0.230

NDI: Neck Disability Index
PCS: Physical-component summary
MCS: Mental-component summary
VAS: Visual Analogue Scale

Improvement of clinical outcome on an individual level demonstrated that a comparable percentage of patients in both groups reported recovery (Table 3 and 4).

Table 3 The number of patients with worse or same results as baseline

	Worse	Same
NDI	6	1
SF-36	7	2
PCS	10	1
MCS	13	1
VAS Neck Pain	12	4
VAS Arm Pain	8	0

NDI: Neck Disability Index
PCS: Physical-component summary
MCS: Mental-component summary
VAS: Visual Analogue Scale

Table 4 The improvement of clinical outcomes

	Normal group	Severe group	P value
NDI	28.0 ± 15.4	27.0 ± 14.3	0.766
SF-36	11.1 ± 6.0	15.4 ± 10.1	0.144
PCS	37.1 ± 16.1	35.0 ± 17.4	0.608
MCS	16.6 ± 21.9	19.2 ± 23.9	0.613
VAS Neck Pain	39.8 ± 24.4	34.9 ± 23.1	0.368
VAS Arm Pain	54.8 ± 22.8	47.7 ± 23.9	0.169

NDI: Neck Disability Index
PCS: Physical-component summary
MCS: Mental-component summary
VAS: Visual Analogue Scale

DISCUSSION

In this study in patients with cervical radiculopathy due to disc herniation who underwent anterior cervical discectomy treatment and who were followed for two years, the size of disc herniation measured on MRI did not correlate to clinical condition at baseline. Neither was the size of the disc herniation correlating to outcome and is thus predictive for clinical outcome after surgical treatment at two-year follow-up.

MRI is indicated in patients with cervical radiculopathy that are either suffering from persistent or progressive neurological findings (including pain) that fail to respond to conservative treatment[21-24], or if malignancy is suspected. MRI is deemed to be not helpful in most cases of cervical radiculopathy because of the high rates of false-negative and false-positive MRI findings. Teresi et al.[25] reported that 57% of patients over the age of 64 years have evidence of disc herniation but do not demonstrate symptoms. Nakashima et al.[8] studied 1,211 asymptomatic volunteers and found that 88% of them had significant disc bulging, being defined as disc protrusion of more than 1 mm. On the contrary, the presence of disc extrusion has been reported to be associated with clinical symptoms, reported by Beattie et al.[26]. In the present study, we demonstrated our results on the patients of symptomatic cervical radiculopathy and studied the size of herniated disc by means of a four-point scale, compared to the previous evaluation of the presence of herniated disc only.

For the patients with cervical radiculopathy, roughly 80-88% of them will improve within four weeks of nonoperative management[22,27]. If severe symptoms persist, spinal surgery as a treatment modality is considered, and it would be interesting if the size of the herniation would correlate to the clinical burden. Our results cannot confirm this. Thus, not only is the presence of a disc herniation on MRI not distinctive for the presence of clinical signs, neither is the size of the hernia indicative for the severity of complaints.

Furthermore, it would be interesting to know whether the size of the disc herniation can predict the postoperative clinical outcome and the perceived recovery after surgical treatment. In a recent systematic review, Hill et al.[28] failed to draw a definitive conclusion on the association between MRI findings of the cervical spine with future neck pain, due to a limited number of included patients, heterogeneity of patients between studies, and the small sample size of the included studies. Moreover, none of the included articles considered outcome after surgical treatment. In agreement with these results, we could neither demonstrate a predictive aspect in the size of disc herniation on clinical outcome.

In lumbar spine the correlation between the size of disc herniation and clinical symptoms was also absent: el Barzouhi et al.[29] demonstrated that the predictive value of the size of disc herniation at baseline in decision making for lumbar disc surgery is absent, and that the size of disc herniation at baseline measured on MRI did not correlate to outcome at one-year follow-up[30]. Eventually, the MRI performed at one-year follow-up in patients with surgical treatment did not distinguish between those with a favourable outcome and those with an unfavourable

outcome[31]. Since one-year follow-up MRIs were not available in the current study on cervical spine, this correlation could not be studied.

A limitation of the current study is that the number of patients is limited. Moreover, the duration of complaints before surgery varied between patients. The time to surgery may have influenced the severity of complaints at baseline. Finally, clinical outcome was only available for the one- and two-year timepoints and it is uncertain whether we would have found similar results at other time points.

CONCLUSIONS

In patients suffering from cervical radiculopathy, the size of disc herniation does not correlate to severity of clinical symptoms at baseline, and does not allow to predict clinical outcome after surgical treatment at two-year follow-up.

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Chapter 4

Prosthesis in Anterior Cervical Herniated Disc Approach Does Not Prevent Radiological Adjacent Segment Degeneration

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Spine

ABSTRACT

Objective

This study aimed to report on the incidence of radiological adjacent segment degeneration (ASD) in patients with cervical radiculopathy due to a herniated disc that were randomized to receive cervical arthroplasty or arthrodesis.

Methods

A total of 253 patients were included in two randomized, double-blinded trials comparing anterior cervical discectomy with arthroplasty (ACDA), with intervertebral cage (ACDF), or without intervertebral cage (ACD) for single-level disc herniation. Neutral lateral radiographs were obtained preoperatively, at one- and two-year follow-up after surgery. ASD was evaluated on x-ray and defined by a decrease in disc height and the presence of anterior osteophyte formation on both the superior and the inferior level in relation to the target level.

Results

ASD was present in 34% of patients at baseline and increased to 59% at two-year follow-up in the arthrodesis groups (ACD and ACDF combined), and to 56% in the arthroplasty group. Progression of ASD was present in 29% of patients in the arthrodesis group and in 31% of patients in the arthroplasty group for two-year follow-up.

Conclusions

Radiological ASD occurs in a similar manner in patients that were subjected to arthrodesis in cervical radiculopathy and in patients that received arthroplasty to maintain motion. Current data tend to indicate that the advantage of cervical prosthesis in preventing radiological ASD is absent.

INTRODUCTION

Anterior cervical discectomy and fusion (ACDF) has been a common surgical treatment for cervical radiculopathy since it was initially described in the 1950s[1-3] and became the gold standard procedure. The procedure remained largely unchanged until the 1990s. Cages, and allograft bone were introduced to reduce the complications of harvesting autologous bone graft from the iliac crest. To decrease the prevalence of pseudarthrosis, plates were successfully introduced[4-6]. However, it was shown that arthrodesis of a motion segment caused by ACDF leads to increased mechanical load at the adjacent levels[7], and hypothetically this can contribute to degeneration of the cervical discs at the adjacent levels (ASD). In the effort to avoid ASD in post-surgical follow-up, artificial disc (ACDA) was developed with the rationale of maintaining motion. Some researchers reported that patients treated with ACDF have higher rates of ASD than those who underwent ACDA during follow-up[8-12]. However, baseline information lacked in most studies. It is highly likely that pre-existing degeneration of the cervical spine, and thus also of the levels adjacent to the operated level, continues, and that the finding of ASD at follow-up is merely the result of pre-existent degeneration with possible additional pre-existing degeneration.

In our clinics, we performed two randomized double-blind trials in which we treated patients with cervical radiculopathy with anterior discectomy. One third of patients received a polyetheretherketone (PEEK) cage in the intervertebral space to restore disc height, leading to fusion of the segments. One third of patients did not receive an intervertebral spacer leading to fusion without restoring disc height and one third of patients received arthroplasty leading to preservation of motion.

The objective of this retrospective cohort study is to compare the incidence of radiological ASD in patients that were enrolled in those two trials.

METHODS

Study design

NECK trial

A prospective, randomized double-blind multicentre trial among patients with cervical radiculopathy due to single-level disc herniation was conducted. Patients were randomly assigned into three groups: anterior cervical discectomy with arthroplasty (ACDA; activC, Aesculap AG, Tuttlingen, Germany), anterior cervical discectomy with fusion (ACDF; Cage standalone) and anterior cervical discectomy without fusion (ACD). The design and study protocol were published previously[13]. The protocol was approved by medical ethics committees, including an approval for randomization after anaesthetic induction. All patients gave informed consent. The two-year follow-up data revealed no differences in clinical outcomes[14].

PROCON trial

The trial design was a prospective, double-blind, single-centre randomized study, with a three-arm parallel group. Patients were randomly allocated into three groups: ACDA (Bryan disc prosthesis, Sofamor Danek, Kerkrade, the Netherlands), ACDF (Cage standalone, DePuy Spine, Johnson and Johnson, Amersfoort, the Netherlands), and ACD. The trial was approved by medical ethics committee and all patients gave informed consent. The design and study protocol were published previously[15]. The follow-up data up to eight years post-surgery revealed no differences in clinical outcomes[16].

Radiological outcomes

Flexion-extension radiographs were obtained preoperatively and at 12 and 24 months post-operatively. The range of motion (ROM) at the index level was defined as the intervertebral sagittal rotation between full flexion and extension. The ROM at index level was measured on dynamic lateral radiographs with a custom developed image analysis tool (BMGO, KU Leuven, Belgium), which has a measurement error of 0.3 degree and 0.3 mm and excellent interrater and intrarater agreement (intraclass correlation coefficient >0.75)[17]. Fusion was defined as ROM less than four degrees[18,19]. Lateral radiographs of the cervical spine were obtained with the patients in a neutral standing position and instructed to look straight ahead, with hips and knees extended. ASD was evaluated based on the height of the adjacent level disc (four grades) and the anterior osteophyte formation (four grades) on x-rays according to the classification reported by Goffin et al.[7] preoperatively, and at 12 and 24 months postoperatively (Table 1).

Table 1 The classification of adjacent segment degeneration

	Disc height	Anterior osteophyte formation
Normal	Same as adjacent disc	No anterior osteophyte
Mild	75-100% of normal disc	Just detectable anterior osteophyte
Moderate	50-75% of normal disc	Clear anterior osteophyte <25% of AP diameter of corresponding vertebral body
Severe	<50% of normal disc	Clear anterior osteophyte >25% of AP diameter of corresponding vertebral body

AP: Anteroposterior

ASD was defined in three different ways:

1) If the patient did not have any loss of disc height and did not have osteophyte formation (*normal)*, the patient was scored as 'non-ASD'. All patients that had loss of disc height, or osteophyte formation, either being *mild*, *moderate* or *severe*, were scored as 'ASD'.
2) If the patient had either no or *mild* loss of disc height (75-100% of the adjacent level, not being the target level) or no or a *mild* osteophyte formation the patient was scored as

'mild-ASD' and all other patients with *moderate* or *severe* loss of disc height or osteophyte formation were scored as 'severe ASD'.

3) In order to evaluate the progression of ASD during follow-up period, the patient was judged as positive if the patient increased in ASD grading during follow-up period. For the patient that did not increase in Goffin score, the ASD progression was marked as negative.

The radiographs were independently evaluated by one senior neurosurgeon dedicated to spine surgery and a junior medical doctor educated for this purpose. If deemed necessary, a third reviewer (senior neurosurgeon) was consulted. The reviewers were blinded to the type of surgery at baseline. The reviewers were not provided with any clinical information of the included patients. Prior to the evaluation of radiographs, the reviewers met in person to evaluate and refine the definitions.

Statistical analysis

All the data were presented as mean ± standard deviation. Baseline and follow-up characteristics of the ACD, ACDF and ACDA treatment group were compared using analysis of variance for continuous data and chi-square test for categorical data. The patients in ACD and ACDF group were combined as 'arthrodesis group', in order to be compared with the patients in 'arthroplasty' group (ACDA). The incidence of ASD between two groups were compared using chi-square test for categorical data. Tests were two tailed, and a P value of < 0.05 was considered significant. SPSS software, version 23.0 was used for all statistical analyses (SPSS, Inc., Chicago, IL, USA).

RESULTS

In the NECK trial, 111 patients were included and randomly assigned to ACD (38 patients), ACDF (38 patients) or ACDA (35 patients). At baseline, X-ray data were available for 107 patients and for 98 patients at two-year follow-up.

In the PROCON trial, 142 patients were randomized into ACD (45 patients), ACDF (47 patients) or ACDA (50 patients). At baseline, X-ray data were available for 121 patients and for 70 patients at two-year follow-up.

Demographics

Baseline characteristics are presented in Table 2. The mean age of the study population was 45.2 years, ranging from 27 to 70 years. There was no difference regarding baseline characteristics between treatment groups. Surgery was most frequent at levels C5-C6 and C6-C7.

Table 2 Patient demographics by treatment arm

		ACD	ACDF	ACDA	Total	P value
Population		83	85	85	253	
Age (years, Mean ± SD)		45.3±6.7	45.6±7.6	44.8±7.7	45.2±7.3	0.787
Body Mass Index (Mean ± SD)		26.2±3.8	26.6±4.7	26.7±4.1	26.5±4.2	0.726
Sex	Male	42	37	43	122	0.939
	Female	41	48	42	131	
Smoking	Yes	33	40	41	118	0.305
	No	50	43	44	133	
Alcohol	Yes	46	52	55	153	0.565
	No	37	31	30	98	
Herniated level						
C4-C5		1	2	0	3	
C5-C6		46	39	40	125	
C6-C7		36	43	45	124	
C7-Th1		0	1	0	1	

ACD: Anterior cervical discectomy
ACDF: Anterior cervical discectomy with fusion
ACDA: Anterior cervical discectomy with arthroplasty
SD: Standard deviation

Fusion rate

If a cut-off value of four degrees movement was taken into consideration, it was demonstrated that 96% of patients in the ACD group (44 patients) and 86% of patients in the ACDF group (38 patients) were fused at two-year follow-up, and that 63% of patients in the ACDA group (36 patients) maintained mobile.

Incidence of adjacent segment degeneration (combined superior with inferior level)

Preoperatively, the incidence of ASD did not differ in the two groups: 37 % in the arthrodesis group (56 patients), and 29% (22 patients) in the arthroplasty group (P=0.2). One year after surgery, the incidence of ASD increased, but was still comparable in the two groups: 47% (59 patients) in the arthrodesis group, and 47% (35 patients) in arthroplasty group (P=0.98). At two-year follow-up, ASD increased to 59% of patients in the arthrodesis group (63 patients), and to 56% (34 patients) in the arthroplasty group. Likewise, there was no statistically significant difference between two groups (P=0.67).

At baseline the incidence of severe ASD was comparable in the two groups: 15% (22 patients) in the arthrodesis group, and 13% (10 patients) in the arthroplasty group (P=0.75). Likewise, at one-year as well as two-year follow-up after surgery, the incidence of ASD still did not differ in the two groups: 22% (28 patients) in the arthrodesis group, and 15% (11

Table 3 Adjacent segment degeneration at superior and inferior level

	Superior Level						Inferior Level					
	Disc height			Osteophyte			Disc height			Osteophyte		
	ACD	ACDF	ACDA	ACD	ACDF	ACDA	ACD	ACDF	ACDA	ACD	ACDF	ACDA
Baseline												
Normal	67 (94.4%)	72 (90%)	71 (93.4%)	52 (73.2%)	59 (73.8%)	60 (80%)	50 (90.9%)	58 (92.1%)	59 (92.2%)	44 (80%)	52 (82.5%)	54 (84.4%)
Mild	4 (5.6%)	8 (10%)	4 (5.3%)	13 (18.3%)	14 (17.5%)	8 (10.7%)	5 (9.1%)	4 (6.3%)	2 (3.1%)	6 (10.9%)	7 (11.1%)	6 (9.4%)
Moderate	0	0	0	5 (7%)	5 (6.3%)	6 (8%)	0	1 (1.6%)	3 (4.7%)	4 (7.3%)	4 (6.3%)	1 (1.6%)
Severe	0	0	1 (1.3%)	1 (1.4)	2 (2.5)	1 (1.3%)	0	0	0	1 (1.8%)	0	3 (4.7%)
1-year												
Normal	60 (92.3%)	51 (85%)	67 (90.5%)	44 (67.7%)	43 (70.5%)	51 (68.9%)	47 (87%)	41 (87.2%)	55 (87.3%)	41 (75.9%)	37 (77.1%)	47 (74.6%)
Mild	5 (7.7%)	7 (11.7%)	6 (8.1%)	14 (21.5%)	11 (18%)	17 (23%)	7 (13%)	5 (10.6%)	5 (7.9%)	5 (9.3%)	6 (12.5%)	10 (15.9%)
Moderate	0	2 (3.3%)	0	4 (6.2%)	5 (8.2%)	4 (5.4%)	0	1 (2.1%)	2 (3.2%)	6 (11.1%)	5 (10.4%)	1 (1.6%)
Severe	0	0	1(1.4%)	3 (4.6%)	2 (3.3%)	2 (2.7%)	0	0	1 (1.6%)	2 (3.7%)	0	5 (7.9%)
2-year												
Normal	50 (89.3%)	43 (86%)	55 (91.7%)	31 (55.4%)	30 (60%)	37 (61.7%)	35 (85.4%)	37 (92.5%)	46 (88.5%)	26 (63.4%)	24 (60%)	37 (71.2%)
Mild	6 (10.7%)	5 (10%)	4 (6.7%)	15 (26.8%)	13 (26%)	17 (28.3%)	6 (14.6%)	2 (5%)	2 (3.8%)	8 (19.5%)	9 (22.5%)	8 (15.4%)
Moderate	0	2 (4%)	0	7 (12.5%)	5 (10%)	4 (6.7%)	0	1 (2.5%)	2 (3.8%)	4 (9.8%)	5 (12.5%)	3 (5.8%)
Severe	0	0	1 (1.7%)	3 (5.4%)	2 (4%)	2 (3.3%)	0	0	2 (3.8%)	3 (7.3%)	2 (5%)	4 (7.7%)

ACD: Anterior cervical discectomy

ACDF: Anterior cervical discectomy with fusion

ACDA: Anterior cervical discectomy with arthroplasty

patients) in the arthroplasty group (P=0.18), respectively, 27% (29 patients) in the arthrodesis group, and 20% (12 patients) in the arthroplasty group (P=0.28).

At one-year follow-up, the proportion of patients with positive ASD progression did not differ in the two groups: 21% (22 patients) of patients demonstrated progression in the arthrodesis group, and 21% (13 patients) in the arthroplasty group (P=0.99). Again, at two years after randomization, the proportion of positive ASD progression was comparable in the two arms (29% in the arthrodesis group (27 patients), and 31% in the arthroplasty group (17 patients; P=0.78)).

An additional analysis in the arthroplasty group, comparing patients that maintained mobile (63%) to patients that demonstrated fusion (although they received a prosthesis (36%)), demonstrated no difference between the groups (ASD, P=0.384; severe ASD, P=0.473; positive ASD progression, P=1.0)

Incidence of adjacent segment degeneration (superior and inferior level respectively)

In the analysis of ASD at superior and inferior level separately, the data on the degree of ASD were demonstrated in Table 3. If ASD was evaluated by the loss of disc height, the incidence of ASD was comparable between arthrodesis and arthroplasty at baseline and at two-year follow-up, at either superior or inferior level (Table 4). When ASD was judged by the presence of anterior osteophyte formation, a similar incidence of ASD was shown between arthrodesis and arthroplasty, both at baseline and at two years after surgery, either at superior level or inferior level (Table 4).

Table 4 Incidence of adjacent segment degeneration at superior and inferior level

		ASD (Defined by loss of disc height)			ASD (Defined by osteophyte formation)		
Level	Follow-up	Arthrodesis	Arthroplasty	P	Arthrodesis	Arthroplasty	P
Superior level	Baseline	12 (7.9%)	5 (6.6%)	0.712	40 (26.5%)	15 (20%)	0.284
	1-year	14 (11.2%)	7 (9.5%)	0.699	39 (31.0%)	23 (31.1%)	0.985
	2-year	13 (12.3%)	5 (8.3%)	0.434	45 (42.5%)	23 (38.3%)	0.604
Inferior level	Baseline	10 (8.5%)	5 (7.8%)	0.877	22 (18.6%)	10 (15.6%)	0.609
	1-year	13 (12.9%)	8 (12.7%)	0.974	24 (23.5%)	16 (25.4%)	0.786
	2-year	9 (11.1%)	6 (11.5%)	0.939	31 (38.3%)	15 (28.8%)	0.265

ACD: Anterior cervical discectomy
ACDF: Anterior cervical discectomy with fusion
ACDA: Anterior cervical discectomy with arthroplasty

DISCUSSION

The rationale of cervical motion preservation technology has been not only maintenance of normal mobility at the index level, but also reduction of accelerated degeneration at adjacent

levels. Based on a recent systematic review[20], the previous research failed to report the incidence of radiological ASD among patients who suffered from radiculopathy exclusively. In this study, we have evaluated the degree of ASD according to the decrease of disc height and the severity of osteophyte formation on x-rays, at both superior and inferior level. We demonstrated that there was no difference in ASD in patients who underwent cervical anterior discectomy with fusion or patients who received an artificial cervical disc, neither at superior nor inferior level.

Disc degeneration and osteophyte formation are physiological processes, and therefore, the observation of degeneration at the adjacent disc levels is not necessarily the result of adjacent segment disease. Particularly in a population with a mean age of 45, it is only the pre-existing degeneration to observe during a degenerative process.

In accordance, our study documented not only ASD in follow-up, but also evaluated degeneration of the cervical spine at the adjacent levels of the target level at baseline. This type of degeneration existed in 34% of the patients at baseline. A similar result was reported previously by Coric et al.[8], who demonstrated that ASD was present in more than 50% of patients before undergoing ACDF or ACDA. Similarly, in the study of Hilibrand et al.[21], 63% of the patients who developed ASD had sign of denegation preoperatively. It is remarkable that only a minority of studies (only in six of the 31 studies that evaluated ASD in published systematic analysis in patients with cervical myelopathy and/or radiculopathy[20]) data on baseline ASD was reported.

It has been suggested before that the addition of a plate to affirm the cage and to further stabilize the two cervical segments may increase the risk of ASD[22]. In a recent systematic review it was discussed that the prevalence of ASD in ACDF is exaggerated in articles from the US, since plating is common there, whereas in Europe, ACDF without a plate is common. It was mentioned that it is an unanswered question whether ASD difference between ACDA and ACDF still exists if ACDF lacks plating[23].This question can be answered in the present study: cage standalone was used in the ACDF approach, and a comparable incidence of ASD was observed between groups.

In the two-year follow-up period of our patients, ASD increased to 58%, irrespective of surgical treatment. It is generally presumed that the development of ASD is a slow process, and that therefore long-term follow-up periods are essential in order to properly judge the occurrence of ASD. Nevertheless, an increase of circa 20% of ASD (or 20% of patients with progression of ASD) in a group of 250 patients, within the first two years after surgery, without a difference between the three groups, justifies the conclusion that ASD is not prevented by the use of cervical prosthesis.

CONCLUSIONS

Cervical disc arthroplasty does not result in less degeneration at the adjacent levels in comparison to patients who were subjected to arthrodesis. The proclaimed advantage of implanting a prosthesis, preventing ASD, is likely to be absent.

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Chapter 5

Maintaining Range of Motion after Cervical Discectomy Does Not Prevent Adjacent Segment Degeneration

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ABSTRACT

Objective

To compare the correlation between range of motion (ROM) of the cervical spine and the presence of radiological adjacent segment degeneration (ASD) after anterior discectomy. Clinical outcome was also correlated to ROM and ASD.

Methods

In all, 253 patients who underwent anterior discectomy for cervical radiculopathy due to a herniated disc were analysed for segmental and global cervical ROM and the presence of ASD both preoperatively, and 12 and 24 months postoperatively. Patients who were included in two randomized, double-blinded trials comparing anterior cervical discectomy with arthroplasty, anterior cervical discectomy with intervertebral cage, or anterior cervical discectomy without intervertebral cage for one level disc herniation were analysed. ROM was defined by a custom-developed image analysis tool. ASD was defined by decrease in disc height and anterior osteophyte formation on x-rays. Clinical outcome was evaluated by means of the Neck Disability Index (NDI).

Results

Two years postoperatively, no correlation was demonstrated between ROM and ASD. The incidence of ASD was comparable in the three groups, being 34% at baseline, and 58% at two-year follow-up. Likewise, ASD progression was comparable in the three treatment arms. No correlation was demonstrated between ROM and NDI or ASD and NDI.

Conclusions

Since ROM is not correlated to ASD, and clinical outcome is not correlated to ROM either, the relevance of continued ROM at the target level seems absent.

INTRODUCTION

It was reported that cervical arthrodesis of a motion segment caused by fusion leads to increased mechanical load at the adjacent levels[1]. Hypothetically this can contribute to degeneration of the cervical discs at the adjacent levels (ASD), which may cause neck pain and disability in follow-up years[2,3]. Some researchers reported that patients treated with anterior cervical discectomy with fusion (ACDF) have higher rates of ASD than those who underwent cervical arthroplasty (ACDA) during follow-up[4-8].

A variety of studies demonstrate that ACDA is able to maintain range of motion (ROM) at the index level[9-13]. Only a limited number of articles reported on the ROM of the whole cervical spine (C2 to C7) and examined whether ACDA affected this differently in comparison to ACDF. Sala et al.[14] and Wang et al.[15] demonstrated similar cervical ROM in both ACDF and ACDA groups at the end of follow-up, but Li et al.[16] and Grasso et al.[17] reported the global cervical ROM in the ACDA group to be larger than that in the ACDF. Although meta-analyses reported that the incidence of ASD was lower in the ACDA than ACDF[18,19], a recent study disputed this and demonstrated that the presence of ASD was similar in the ACDA and ACDF at five-year follow-up, both clinically and radiologically[20]. Additionally, the problem with the vast majority of studies is that the level of evidence is low to very low, since risk of bias is high, methods to assess ROM are insufficiently precise, and results are contradictory[21].

The objective of the current study is to study ROM in patients who were included in two randomized double-blind trials on patients treated by anterior cervical discectomy with or without interbody fusion and arthroplasty for cervical radiculopathy. The correlation between ROM at the index level and the presence of ASD was studied. The ROM at the index level was compared between the surgical methods, as well as the ROM of the total cervical spine. Moreover, ASD and ROM were correlated to neck disability.

METHODS

Study design

This is a retrospective cohort study using data from two prospective, randomized double-blind trials: the NECK trial and the PROCON trial.

NECK trial

A prospective, randomized double-blind multicentre trial among patients with cervical radiculopathy due to single-level disc herniation was conducted. Patients were randomly assigned into three groups: anterior cervical discectomy with arthroplasty (ACDA; activC, Aesculap AG, Tuttlingen, Germany), anterior cervical discectomy with fusion (ACDF; Cage standalone) and anterior cervical discectomy without fusion (ACD). Patients (age 18 to

65-year-old) with radicular signs and symptoms in one or both arms for at least eight weeks, in who conservative therapy failed were eligible for inclusion. All patients were diagnosed with cervical radiculopathy by a neurologist in one of the participating hospitals. If MRI demonstrated a single-level cervical disc herniation with or without osteophyte at one level (C3-C4 to C7-Th1) in accordance with clinical signs and symptoms, patients could be included as surgical candidates for the study by the consulting neurosurgeon. Patients with previous cervical surgery, absence of motion or increased anteroposterior translation or very narrow (< 3 mm) intervertebral space or severe segmental kyphosis (> 3 degrees) at the index level on static or dynamic x-rays, neck pain only or symptoms, and signs of chronic myelopathy were excluded. A randomized design with variable block sizes was used, with allocations stratified according to centre. The protocol was approved by medical ethics committees, including an approval for randomization after anaesthetic induction. All patients gave informed consent.

The design and study protocol were published previously[22]. The two-year follow-up data revealed no differences in clinical outcomes[23].

PROCON trial

The trial design was a prospective, double-blind, single-centre randomized study, with a three-arm parallel group. Patients were randomly allocated into three groups: ACDA (Bryan disc prosthesis, Sofamor Danek, Kerkrade, the Netherlands), ACDF (Cage standalone, DePuy Spine, Johnson and Johnson, Amersfoort, the Netherlands), and ACD. Patients (age 18 to 55-year-old) were eligible for inclusion with monoradicular syndrome in the arm due to one-level cervical disc degeneration disease and/ or an osteophyte at MRI. The radiological findings should be in accordance with the clinical presentation. The patients with myelopathy, previous cervical surgery, psychiatric, or mental disease were excluded. The trial was approved by medical ethics committee. All patients gave informed consent.

The design and study protocol were published previously[24]. The follow-up data up to eight years post-surgery revealed no differences in clinical outcomes[25].

Clinical outcome measurement

Neck disability index (NDI) is a 10-item questionnaire on 3 different aspects: pain intensity, daily work-related activities and nonwork-related activities. Each item is scored from 0 to five and the total score ranges from 0 (best score) to 50 (worst score). This 50-point score was converted to a percentage (50 points=100%). The NDI is a modification of the Oswestry Low Back Pain Index and has been shown to be reliable and valid for patients with cervical pathology[26-28].

Radiological outcomes

Flexion-extension radiographs were obtained preoperatively and at 12 and 24 months postoperatively. The ROM at the index level and of the total cervical spine (C2 to C7) were

measured. The ROM at the index level was defined as the intervertebral sagittal rotation between full flexion and extension. The ROM at the index level was measured on dynamic lateral radiographs with a custom-developed image analysis tool (BMGO, KU Leuven, Belgium), which has a measurement error of 0.3 degree and 0.3 mm and excellent interrater and intrarater agreement (intraclass correlation coefficient >0.75)[29]. Fusion was defined as ROM less than 4 degrees[30,31]. The Cobb angle of C2 to C7 was measured by the lines drawn parallel to the caudal endplate of C2 and C7.

Standing lateral radiographs of the cervical spine were obtained with the patients in a neutral standing position and instructed to look straight ahead, with hips and knees extended.

ASD was evaluated based on the height of the adjacent level disc and the anterior osteophyte formation on X-rays according to the classification reported by Goffin et al.[1] preoperatively and at 12 and 24 months postoperatively (Table 1). Only if neither the superior nor inferior adjacent level demonstrated loss of disc height or anterior osteophyte formation, the patient was graded as 'non-ASD'. Additionally, in a separate analysis, 'severe ASD' was defined as in patients with the classification 'moderate' or 'severe' loss of disc height or anterior osteophyte formation in either the superior or inferior level. Finally, in order to study progression of adjacent level degeneration, 'ASD progression' was marked as positive or negative for patients who did or did not increase in Goffin score during follow-up.

Table 1 The classification of adjacent segment degeneration

	Disc height	Anterior osteophyte formation
Normal	Same as adjacent disc	No anterior osteophyte
Mild	75-100% of normal disc	Just detectable anterior osteophyte
Moderate	50-75% of normal disc	Clear anterior osteophyte <25% of AP diameter of corresponding vertebral body
Severe	<50% of normal disc	Clear anterior osteophyte >25% of AP diameter of corresponding vertebral body

AP: Anteroposterior

The radiographs were independently evaluated by one senior neurosurgeon dedicated to spine surgery and a junior medical doctor educated for this purpose. The reviewers were not provided with any clinical information of the included patients. Before the evaluation of radiographs, the reviewers met in person to evaluate and refine the definitions.

Correlating range of motion to adjacent segment degeneration

In order to study the relationship between ROM and ASD, subjects were dichotomized according to the presence of ASD, irrespective of the surgical method. ROM can be studied as ROM at the index level or ROM of the total cervical spine. ASD can be studied as 'non-ASD' versus 'ASD', as 'mild ASD' versus 'severe ASD', or as 'negative progression of ASD' versus 'positive progression of ASD'.

Statistical analysis

Patients in the NECK trial and the PROCON trial were subject of this study. All the data were presented as mean ± standard deviation. Baseline and follow-up characteristics of the ACD, ACDF and ACDA treatment group were compared using analysis of variance for continuous data and chi-square test for categorical data. Student *t*-test was used to compare continuous data between groups. Logistic regression tests were applied to evaluate correlations between ROM and ASD and ROM and NDI. Chi-square tests or Fisher's exact test were applied to correlate the dichotomized ROM at the target level to the presence of ASD. Tests were two tailed, and a P value of < 0.05 was considered significant. SPSS software, version 23.0 was used for all statistical analyses (SPSS, Inc., Chicago, IL, USA).

RESULTS

In the NECK trial, 111 patients were included and randomly assigned to ACD (38 patients), ACDF (38 patients) or ACDA (35 patients). At baseline, X-ray data were available for 107 patients and for 98 patients at two-year follow-up.

In the PROCON trial, 142 patients were randomized into ACD (45 patients), ACDF (47 patients), or ACDA (50 patients). At baseline, X-ray data were available for 121 patients and for 70 patients at two-year follow-up.

Demographics

Baseline characteristics are presented in Table 2. The mean age of the study population was 45.2 ± 7.3 years, ranging from 27 to 70 years. There was no difference regarding baseline characteristics between treatment groups. Surgery was most frequent at levels C5-C6 and C6-C7.

Range of motion

In Figure 1, the segmental ROM were not statistically different at baseline (P=0.744). At both one- and two-year follow-up, the ROM at the index level of patients with ACDA was significantly higher than the ROM in patients with ACD and ACDF (P<0.001, Table S1).

ROM at the target level was not consequently absent ('fused') in the ACD and ACDF groups, and not consequently maintained ('mobile') in the ACDA group. If a cut-off value of 4 degrees movement was taken into consideration, it was demonstrated that 96% of patients in the ACD group and 86% of patients in the ACDF group were fused at two years' follow-up, and that 63% of patients in the ACDA group maintained mobile (Table 3). If the 63% of patients in the ACDA group who maintained mobile were considered, the ROM at the target level was 10.1 ± 3.9 degrees.

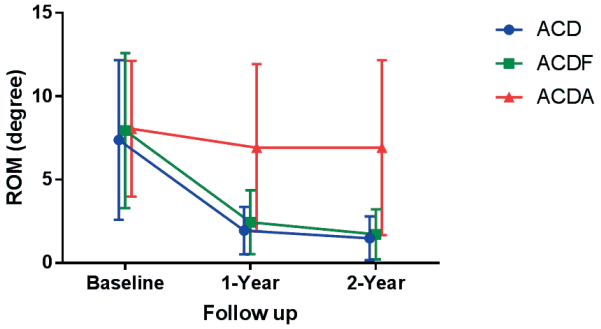

Figure 1 Range of motion of the index level

Table 2 Patient demographics

	ACD	ACDF	ACDA	Total	P value
Population	83	85	85	253	-
Age (years, Mean ± SD)	45.3 ± 6.7	45.6 ± 7.6	44.8 ± 7.7	45.2 ± 7.3	0.787
BMI (Mean ± SD)	26.2 ± 3.8	26.6 ± 4.7	26.7 ± 4.1	26.5 ± 4.2	0.726
Sex (Male)	42	37	43	122	0.939
Smoking	33	40	41	118	0.305
Alcohol	46	52	55	153	0.565
Herniated level					
C4-C5	1	2	0	3	-
C5-C6	46	39	40	125	-
C6-C7	36	43	45	124	-
C7-Th1	0	1	0	1	-

ACD: Anterior cervical discectomy
ACDF: Anterior cervical discectomy with fusion
ACDA: Anterior cervical discectomy with arthroplasty
SD: Standard deviation
BMI: Body Mass Index

Table 3 Patients with fusion (range of motion<4 degrees)

Follow-up	ACD	ACDF	ACDA	Total
1-year follow-up	91.5%	79.6%	33.8%	66.5%
2-year follow-up	95.7%	86.4%	36.8%	70.1%

ACD: Anterior cervical discectomy
ACDF: Anterior cervical discectomy with fusion
ACDA: Anterior cervical discectomy with arthroplasty

In Figure 2, ROM of the total cervical spine was comparable for all patients at baseline (P=0.523). The patients in the ACDA group had a higher global ROM than those in the ACD group and ACDF group, at both one- and two-year follow-up (P<0.001 and P=0.016, Table S1).

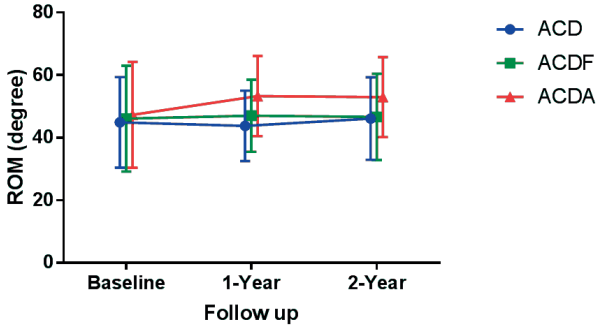

Figure 2 Range of motion of the total cervical spine

Adjacent segment degeneration

The incidence of ASD was summarized in Table 4. No significant difference could be detected between three treatment arms at both baseline, one- and two-year follow-up, neither the incidence of ASD nor the incidence of severe ASD. Similarly, positive progression of ASD were comparable between three groups at one year and two years after surgery.

Correlation between range of motion to adjacent segment degeneration

At two-year follow-up, no correlation between segmental ROM and the presence of ASD was demonstrated (P=0.766). Neither was there such a correlation if the ROM of the whole cervical spine was considered (P=0.087). Moreover, neither segmental ROM nor global ROM was correlated with either severe ASD or positive progression of ASD (P>0.05).

Table 4 The incidence of adjacent segment degeneration

		ACD	ACDF	ACDA	Total	P value
ASD	Baseline	38.0% (27)	36.3% (29)	28.6% (22)	34.2% (78)	0.428
	1-year FU	49.2% (32)	44.3% (27)	46.7% (35)	46.8% (94)	0.855
	2-year FU	62.5% (35)	54.9% (28)	55.7% (34)	57.7% (97)	0.674
Severe ASD	Baseline	15.5% (11)	13.8% (11)	13.0% (10)	14.0% (32)	0.905
	1-year FU	21.5% (14)	23.0% (14)	14.5% (11)	19.3% (39)	0.393
	2-year FU	28.6% (16)	25.5% (13)	19.7% (12)	24.4% (41)	0.522
Positive ASD progression	1-year FU	24.5% (13)	17.3% (9)	21.0% (13)	21.0% (35)	0.662
	2-year FU	32.6% (15)	25.0% (12)	30.9% (17)	29.5% (44)	0.693

ASD: Adjacent segment degeneration
ACD: Anterior cervical discectomy
ACDF: Anterior cervical discectomy with fusion
ACDA: Anterior cervical discectomy with arthroplasty
FU: Follow-up

As we stated above, 63% of patients with ACDA had radiographic preserved ROM (>4 degrees) versus 37% who did not at two-year follow-up. In the ACDA group exclusively, no correlation could be demonstrated between preserved ROM and the presence of ASD, severe ASD, nor positive ASD progression (Table 5).

Table 5 Adjacent segment degeneration and range of motion in the ACDA group

	Mobile*	Fused#	P
ASD	31.6% (18)	22.8% (13)	0.384
Non-ASD	31.6% (18)	14.0% (8)	
Severe ASD	8.8% (5)	8.8% (5)	0.473
Mild ASD	54.4% (31)	28.1% (16)	
Positive ASD progression	17.6% (9)	9.8% (5)	1.0
Negative ASD progression	49.0% (25)	23.5% (12)	

ASD: Adjacent segment degeneration
ACDA: Anterior cervical discectomy with arthroplasty
*: Range of motion more than 4 degrees
#: Range of motion less than 4 degrees

Furthermore, if the patients were studied irrespective of surgical method, no significant correlation could be detected between preserved ROM and ASD, with the exception of the two-year results, if ASD is dichotomized in 'mild ASD' and 'severe ASD' (P=0.042; Table 6).

Table 6 Adjacent segment degeneration and range of motion

		ASD	Non-ASD	P value	Severe ASD	Mild ASD	P value	Positive ASD progression	Negative ASD progression	P value
1-year FU	Mobile*	14.8% (25)	19.5% (33)	0.493	5.3% (9)	29.0% (49)	0.493	5.0% (7)	32.4% (45)	0.072
	Fused #	32.0% (54)	33.7% (57)		13.0% (22)	52.7% (89)		16.5% (23)	46.0% (64)	
2-year FU	Mobile*	14.4% (21)	15.8% (23)	0.115	4.1% (6)	26.0% (38)	0.042	8.6% (11)	24.2% (31)	0.636
	Fused #	43.2% (63)	26.7% (39)		20.5% (30)	49.3% (72)		20.3% (26)	46.9% (60)	

ASD: Adjacent segment degeneration
FU: Follow-up
*: Range of motion more than 4 degrees
#: Range of motion less than 4 degrees

Correlation between range of motion and neck disability

If the 4 degrees cut-off value for ROM at the index level was used to study the correlation between ROM and NDI, no significant correlation could be demonstrated, neither at baseline, one-year nor two-year follow-up (P>0.05).

Correlation between adjacent segment degeneration and neck disability

No correlation was found between neck disability with the presence of ASD, mild ASD nor positive ASD progression (Table 7).

Table 7 Adjacent segment degeneration and neck disability index

	ASD	Non-ASD	P value
Baseline	40.3 ± 15.1	39.2 ± 15.6	0.615
1-year FU	14.5 ± 13.8	15.8 ± 16.4	0.593
2-year FU	16.0 ± 16.8	16.6 ± 16.3	0.837
	Severe ASD	Mild ASD	P value
Baseline	40.6 ± 12.7	39.4 ± 15.8	0.668
1-year FU	13.8 ± 13.7	15.5 ± 15.5	0.578
2-year FU	18.2 ± 15.5	15.6 ± 15.5	0.438
	Positive ASD progression	Negative ASD progression	P value
1-year FU	15.4 ± 14.8	14.1 ± 14.0	0.704
2-year FU	15.9 ± 15.1	16.5 ± 16.4	0.864

ASD: Adjacent segment degeneration
FU: Follow-up

DISCUSSION

The rationale for cervical motion preserving devices is to reduce accelerated degeneration at adjacent levels. It is thought that this will result in reduction of ASD and better functional outcome in the long term. We demonstrated that ROM, neither at the target level nor of the whole cervical spine, was correlated to ASD two years after surgery. Moreover, we demonstrated that there was no difference in ASD in patients who were subjected to cervical anterior discectomy with fusion and patients that received a prosthesis, which is in line with the recent published results of MacDowall et al.[20], who demonstrated that clinical and radiological ASD were comparable between fusion and arthroplasty cohorts. In some patients, accelerated degeneration at the adjacent levels can lead to clinical symptoms, like neck pain, radiculopathy, and disability, which can be represented by the NDI value. In agreement with earlier reports[23] in which the NDI was demonstrated not to differ between the ACD, ACDF and ACDA treatment arms, ASD did not demonstrate a correlation to NDI.

In the ACDA group, 63% patients with a preserved ROM (> 4 degrees) did not show a significantly lower incidence of ASD or less positive ASD progression than patients with an immobile cervical segment. Therefore, the rationale for cervical motion preserving devices to reduce accelerated degeneration at the adjacent levels is not confirmed in the present study.

Disc degeneration and osteophyte formation are physiological processes, and therefore some extent of degeneration at the adjacent disc levels is expected to be already present at baseline in a population with a mean age of 45. In accordance, our study documented that this

type of degeneration existed in 34% of the patients at baseline. A similar result was reported previously by Coric et al.[4], who demonstrated that ASD was present in more than 50% of patients before undergoing ACDF or ACDA. In the two-year follow-up period of our patients, the ASD increased to 58%, irrespective of surgical treatment. It is generally presumed that the development of ASD is a slow process, and that therefore long-term follow-up periods are essential in order to properly judge the occurrence of ASD. Nevertheless, an increase of circa 20% of ASD (or 20% of patients with progression of ASD) in a group of 250 patients, within the first two years after surgery, without a difference between the three groups, justifies the conclusion that ASD is not significantly dependent on ROM of the target level. Our results are in contradiction to several studies demonstrating that ACDA results in a lower incidence of ASD[4-8,32] in comparison to ACDF. However, the majority of these studies failed to provide ASD information on baseline, introducing selection bias.

A limitation of the current study may be that determining ROM on x-ray will depend on the ability and willingness of the patients to reach full flexion and extension of the cervical spine. Unfortunately, there is no method to improve it. The quality of X-ray is important as well, because the angles will be influenced by angling of the cervical vertebrae in the coronal plane. Another flaw is the focus on radiological ASD. Clinical ASD would be represented by invalidating radicular symptoms due to a herniated disc at the adjacent level. In ultimo, if these complaints would be significantly invalidating, subsequent surgery would follow. The number of reoperations in the three groups for this diagnosis would therefore be a suitable measure for clinical ASD. In an earlier publication, Donk et al.[33] showed that reoperations were more prevalent in the ACDF group than in the other two groups, but that differences were very small. Likewise, in the NECK trial, reoperation rates were very low. Therefore, numbers are too small to draw meaningful conclusions.

CONCLUSIONS

ROM is not correlated to ASD, and clinical outcome is not correlated to ROM following anterior cervical discectomy. Therefore, the relevance of maintaining ROM at the index level seems absent. However, the follow-up of two years may be too short to draw firm conclusions.

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Table S1 Range of motion

		ACD	ACDF	ACDA	P value
Index ROM	Baseline	7.4 ± 4.8	7.9 ± 4.7	8.1 ± 4.1	0.744
	1-year FU	1.9 ± 1.4	2.4 ± 1.9	6.9 ± 5.0	<0.001
	2-year FU	1.5 ± 1.3	1.7 ± 1.5	6.9 ± 5.3	<0.001
Global ROM	Baseline	43.9 ± 14.9	47.4 ± 16.3	47.3 ± 16.9	0.523
	1-year FU	43.8 ± 11.3	47.1 ± 11.6	53.3 ± 12.8	0.001
	2-year FU	46.1 ± 13.2	46.6 ± 13.9	52.9 ± 12.9	0.016

ACD: Anterior cervical discectomy
ACDF: Anterior cervical discectomy with fusion
ACDA: Anterior cervical discectomy with arthroplasty
ROM: Range of motion
FU: Follow-up

Chapter 6

The Association of Cervical Sagittal Alignment with Adjacent Segment Degeneration

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ABSTRACT

Objective

Cervical spine surgery may affect sagittal alignment parameters and induce accelerated degeneration of the cervical spine. Cervical sagittal alignment parameters of surgical patients will be correlated with radiological adjacent segment degeneration (ASD) and with clinical outcome parameters.

Methods

Patients were analysed from two randomized, double-blinded trials comparing anterior cervical discectomy with arthroplasty, with intervertebral cage, and without intervertebral cage. C2-C7 lordosis, T1 slope, C2-C7 sagittal vertical axis and the occipito-cervical inclination (OCI) were determined as cervical sagittal alignment parameters. Radiological ASD was scored by the combination of decrease in disc height and anterior osteophyte formation. Neck disability index (NDI), physical component summary (PCS) and mental component summary (MCS) of 36-Item Short Form Health Survey were evaluated as clinical outcomes.

Results

The cervical sagittal alignment parameters were comparable between the three treatment groups, both at baseline and at two-year follow-up. Irrespective of surgical method, C2-C7 lordosis was found to increase from 11 to 13 degrees, but the other parameters remained stable during follow-up. Only the OCI was demonstrated to be associated with the presence and positive progression of radiological ASD, both at baseline and at two-year follow-up. NDI, PCS and MCS were demonstrated not to be correlated to cervical sagittal alignment. Likewise, a correlation with the value or change of the OCI was absent.

Conclusions

OCI, an important factor to maintain horizontal gaze, was demonstrated to be associated with radiological ASD, suggesting that the occipito-cervical angle influences accelerated cervical degeneration. Since OCI did not change after surgery, degeneration of the cervical spine may be predicted by the value of OCI.

INTRODUCTION

The cervical spine has a crucial role in compensating a distorted global spinal balance. In order to maintain horizontal gaze, the cervical spine will compensate[1]. Regularly, global sagittal imbalance is only present in a very mild form, and subsequently, cervical compensation is only minor. However, even minor cervical spine balance compensation mechanisms may cause accelerated degeneration of the cervical spine segments (ASD). Surgical interventions that possibly interfere with sagittal alignment, like anterior discectomy, may influence ASD, irrespective of the presence of preoperative sagittal imbalance of the whole spine.

In order to quantify cervical spine sagittal alignment, several radiographic parameters have been proposed, including C2-C7 lordosis, C2-C7 sagittal vertical axis (SVA) and T1 slope[2,3]. It has to be realised though that these parameters also importantly influence each other[4,5].

Furthermore, occipito-cervical inclination (OCI), defining the occipito-cervical angle, independent of the occipito-cervical distance, is an important sagittal alignment parameter, since it represents the stress on the cervical spine to maintain horizontal gaze[6]. To the best of our knowledge, no study correlated this parameter with cervical ASD previously.

Anterior cervical discectomy and fusion (ACDF) has been a common surgical treatment for cervical radiculopathy since it was initially described in the 1950s[7,8] and became the gold standard procedure. Recently, artificial disc implantation (ACDA) has been proposed to maintain disc height, restore cervical motion and avoid neck pain and disability in post-surgical follow-up[9]. Limited studies have described the cervical sagittal alignment after ACDA in comparison with ACDF and reported contradictory results. Kim et al.[10] reported that ACDA maintained the cervical sagittal alignment well in comparison to ACDF, but other researchers disputed this advantage and found that the alignment of the cervical spine is unaltered irrespective of the anterior cervical discectomy procedure performed[11,12]. Most studies, however, only focused on comparing the cervical curvature between ACDF and ACDA, and the other sagittal alignment parameters were rarely investigated.

In the current study, sagittal alignment parameters of the cervical spine are evaluated in patients from two randomized double-blind trials on patients treated by anterior cervical discectomy with or without interbody fusion and arthroplasty for cervical radiculopathy at baseline and at two-year follow-up. The parameters and the changes in sagittal alignment were correlated with the incidence and progression of radiological ASD and to clinical outcomes.

METHODS

Study design

NECK trial

A prospective, randomized double-blind multicentre trial among patients with cervical radiculopathy due to single-level disc herniation was conducted. Patients were randomly assigned into three groups: anterior cervical discectomy with arthroplasty (ACDA; activC, Aesculap AG, Tuttlingen, Germany), anterior cervical discectomy with fusion (ACDF; Cage standalone) and anterior cervical discectomy (ACD). The protocol was approved by medical ethics committees, including an approval for randomization after anaesthetic induction. All patients gave informed consent.

The design and study protocol were published previously[13]. The two-year follow-up data revealed no differences in clinical outcomes[14].

PROCON trial

The trial design was a prospective, double blind, single-centre randomized study, with a three-arm parallel group. Patients were randomly allocated into three groups: ACDA (Bryan disc prosthesis, Sofamor Danek, Kerkrade, the Netherlands), ACDF (Cage standalone, DePuy Spine, Johnson and Johnson, Amersfoort, the Netherlands), and ACD. The trial was approved by the medical ethics committee. All patients gave informed consent.

The design and study protocol were published previously[15]. The follow-up data up to eight years post-surgery revealed no differences in clinical outcomes[16].

Radiological evaluation

Lateral x-rays of the cervical spine were obtained with the patients in a standing position and instructed to look straight ahead, with hips and knees extended, in order to obtain a neutral position of the head.

Sagittal alignment parameters

Cervical sagittal alignment parameters were measured preoperatively and two years postoperatively (Figure 1):

- C2-7 lordosis: the angle as measured between the lines drawn parallel to the caudal endplate of C2 and C7.
- C2-7 SVA: distance between a plumb line from the centre of the C2 vertebra to the plumb line from the centre of C7 vertebra.
- T1 slope: since the superior endplate of T1 vertebra is invisible for most patients, C7 slope was measured as the angle between the superior endplate of C7 and a horizontal reference line. Subsequently, this angle was converted to the T1 slope using the formula: T1 slope= (C7 slope+0.54)/ 0.88[17].

- OCI: the angle formed by the line connecting the posterior vertical border of the C4 vertebral body and McGregor's line[6].

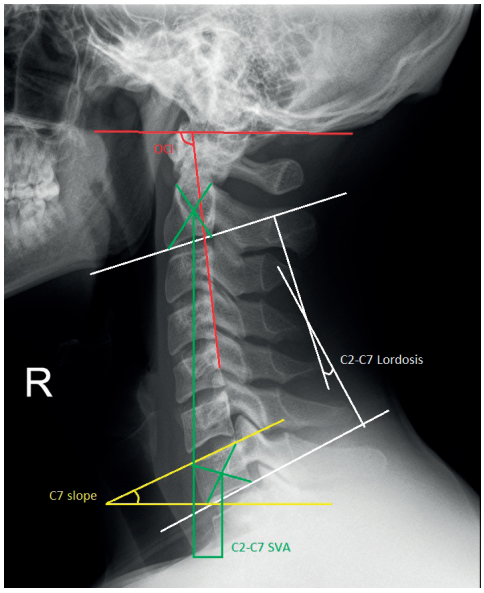

Figure 1 Radiographic evaluation of cervical sagittal alignment parameters

The changes of sagittal parameters after surgery, with reference to the baseline values, were investigated as well.

In the ACD group, the disc height decreased from the pre- to the post-operative situation. This might therefore influence the sagittal alignment parameters. Additionally, for this group specifically, the disc height was correlated to the baseline and two-year follow-up alignment parameters as well.

Adjacent segment degeneration

ASD was defined based on the height of an adjacent level disc and the anterior osteophyte formation on x-rays according to the classification reported by Goffin et al.[18] preoperatively and 24 months post-operatively (Table 1). Since there are no strict criteria to define ASD, evaluation of ASD was performed with three different methods. Firstly, only if neither the superior nor inferior adjacent level demonstrated loss of disc height or anterior osteophyte formation, the patient was graded as 'non-ASD'; all other patients were graded as 'ASD'. Secondly, in a separate analysis, 'mild-ASD' was scored if patients had 'no' or 'minor' ASD changes in both the superior and inferior adjacent levels, and 'ASD' was defined to be present if the classification was 'moderate' or 'severe' loss of disc height or anterior osteophyte formation in either the superior or inferior level. Thirdly, ASD was evaluated by progression

of adjacent level degeneration: 'ASD progression' was marked as positive or negative for patients that did or did not increase in Goffin score during follow up.

Table 1 The classification of adjacent segment degeneration

	Disc height	Anterior osteophyte formation
Normal	Same as adjacent disc	No anterior osteophyte
Mild	75-100% of normal disc	Just detectable anterior osteophyte
Moderate	50-75% of normal disc	Clear anterior osteophyte <25% of AP diameter of corresponding vertebral body
Severe	<50% of normal disc	Clear anterior osteophyte >25% of AP diameter of corresponding vertebral body

AP: Anteroposterior

Clinical outcomes

Neck disability index (NDI) is a 10-item questionnaire on three different aspects: pain intensity, daily work-related activities and nonwork-related activities. Each item is scored from 0 to 5 and the total score ranges from 0 (best score) to 50 (worst score). This 50 points score was converted to a percentage (50 points=100%). The NDI is a modification of the Oswestry Low Back Pain Index and has been shown to be reliable and valid for patients with cervical pathology[19]. The physical component summary (PCS) and mental component summary (MCS) are derived from the 36-Item Short Form Health Survey and are summary scores for, respectively, the Physical Quality of Life and the Mental Quality of Life. The PCS and MCS range from 0 to 100, with higher scores representing better self-reported health.

Statistical analysis

All the data were presented as mean ± standard deviation. Paired *t*-test was used to compare the changes of sagittal alignment parameters between baseline to two-year follow-up data. Logistic regression analysis was used to determine the correlation between the sagittal balance parameters at baseline with the presence and progression of ASD. Likewise, logistic regression analysis was used to determine the correlation between the changes in sagittal balance parameters during the two-year follow-up time. Linear regression analysis was used to correlate the disc height and cervical sagittal alignment parameters at baseline and at two-year follow-up in the ACD group. Linear regression analysis was also performed to correlate the clinical outcome data with the sagittal balance parameters at two-year follow-up in all groups. The correlations between sagittal alignment parameters were analysed using the Pearson correlation coefficient.

A P value of < 0.05 was considered significant. SPSS software, version 23.0, was used for all statistical analyses (SPSS, Inc., Chicago, IL, USA).

RESULTS

In the current study, 253 patients were included and randomly assigned to ACD (83 patients), ACDF (85 patients) or ACDA (85 patients). At baseline, x-ray data were available for 228 patients and for 168 patients at two-year follow-up.

Demographics

Baseline characteristics are presented in Table 2. The mean age of the study population was 45.2 ± 7.3 years, ranging from 27 to 70 years. There was no difference regarding baseline characteristics between treatment groups. Surgery was most frequently at levels C5-C6 and C6-C7.

Table 2 Patient demographics by treatment arm

		ACD	ACDF	ACDA	Total	P value
Population		83	85	85	253	
Age (years, Mean ± SD)		45.3±6.7	45.6±7.6	44.8±7.7	45.2±7.3	0.787
Body Mass Index (Mean ± SD)		26.2±3.8	26.6±4.7	26.7±4.1	26.5±4.2	0.726
Sex	Male	42	37	43	122	0.939
	Female	41	48	42	131	
Smoking	Yes	33	40	41	118	0.305
	No	50	43	44	133	
Alcohol	Yes	46	52	55	153	0.565
	No	37	31	30	98	
Herniated level						
C4-C5		1	2	0	3	
C5-C6		46	39	40	125	
C6-C7		36	43	45	124	
C7-Th1		0	1	0	1	

ACD: Anterior cervical discectomy
ACDF: Anterior cervical discectomy with fusion,
ACDA: Anterior cervical discectomy with arthroplasty
SD: Standard deviation

Characteristics of cervical sagittal alignment in subgroups

Table 3 demonstrates the characteristics of the cervical sagittal alignment parameters in the different treatment arms. No differences were found regarding sagittal alignment parameters between the three surgical groups neither at baseline nor at two-year follow-up (P>0.05). Additionally, it was found that the cervical alignment parameters did not change significantly comparing baseline to post-operative values, with the exception of C2-C7 lordosis in the ACDF group (P=0.048). Irrespective of the surgical method, only C2-C7 lordosis was found to change (increase) significantly over two years (from 11.3 to 13.1 degrees, P=0.023). The

other three parameters (OCI, C2-C7 SVA and T1 slope) did not change with a statistical significance. Notably, the angle or sloped could be minimally negatively or minimally positively deviating.

Table 3 Characteristics of sagittal alignment parameters in subgroups

	Lordosis	SVA	T1 slope	OCI
Baseline				
ACD (63)	12.6±9.6	21.9±12.9	28.1±10.3	105.7±9.1
ACDF (69)	9.5±8.6	23.5±11.2	30.1±8.4	104.6±9.5
ACDA (69)	12.1±9.0	22.1±10.8	30.6±9.0	104.7±8.7
P value	0.117	0.684	0.272	0.803
2-year follow-up				
ACD (48)	13.5±9.8	21.0±11.2	30.7±10.1	106.4±8.4
ACDF (48)	11.8±11.1	24.1±10.5	33.1±8.7	106.9±10.5
ACDA (57)	13.6±10.5	21.9±11.9	30.6±10.0	105.1±11.3
P value	0.634	0.376	0.349	0.663

SVA: Sagittal vertical axis
OCI: Occipito-cervical inclination
ACD: Anterior cervical discectomy
ACDF: Anterior cervical discectomy with fusion
ACDA: Anterior cervical discectomy with arthroplasty

Correlation between disc height and cervical sagittal alignment

In the ACD group, there was no correlation between the disc height of the target level and cervical sagittal alignment at baseline (P>0.05). Likewise, this correlation was absent at two-year follow-up (P>0.05). There was a decrease in disc height, but this did not impact overall balance.

Adjacent segment degeneration

Preoperatively, the incidence of ASD did not differ in the three groups: 38% in the ACD group (27 patients), 36% (29 patients) in the ACDF group, and 29% (22 patients) in the ACDA group (P=0.428). At two-year follow-up, ASD increased to 63% of patients in the ACD group (35 patients), and 55% (28 patients) in the ACDF group, and to 56% (34 patients) in the ACDA group. Likewise, between three groups, there was no statistically significant difference (P=0.674).

If ASD was considered to be scored as 'ASD' only if disc degeneration and/or presence of osteophytes was moderate or severe, the incidence of ASD was still comparable in the three treatment arms at baseline: 16% in the ACD group, 14% in the ACDF group, and 13% in the ACDA group (P=0.905). And likewise, two years after surgery, the incidence of ASD did not differ between three groups (29% in the ACD group, 26% in the ACDF group and 20% in the ACDA group; P=0.522).

Furthermore, the progression of ASD was also investigated, comparing follow-up to baseline data. At two years after surgery, the proportion of positive ASD progression was comparable in the three treatment arms (33% in the ACD group, 25% in the ACDF group and 31% in the ACDA group; P=0.693).

Correlation between cervical sagittal alignment and radiological adjacent segment degeneration

In order to study the relationship between cervical sagittal alignment parameters and ASD, subjects were dichotomized according to the presence and progression of radiological ASD, irrespective of the surgical method. The average values of sagittal alignment parameters of subjects with and without ASD are shown in Table 4.

Table 4 Cervical sagittal alignment parameters with the presence and progression of adjacent segment degeneration

	ASD	Non-ASD	P value	ASD	Mild-ASD	P value	ASD positive progression	ASD negative progression	P value
Baseline									
Lordosis	10.8±9.4	11.6±9.0	0.568	12.7±9.5	11.1±9.1	0.412	-	-	-
SVA	22.7±12.4	22.5±11.3	0.884	25.8±11.3	22.1±11.6	0.122	-	-	-
T1 slope	29.8±8.8	29.5±9.5	0.879	32.1±8.7	29.2±9.3	0.144	-	-	-
OCI	107.7±9.0	103.7±8.9	0.007*	108.7±8.0	104.4±9.1	0.040*	-	-	-
2-year follow-up									
Lordosis	11.5±10.2	14.8±10.5	0.054	10.8±9.3	13.7±10.7	0.130	11.2±9.6	14.7±11.0	0.085
SVA	23.2±11.1	21.1±11.5	0.270	24.8±11.8	21.5±11.0	0.118	23.2±11.5	21.4±11.3	0.423
T1 slope	31.0±9.7	32.1±9.6	0.492	31.3±8.9	31.5±9.9	0.898	29.7±8.1	32.5±10.1	0.139
OCI	109.0±10.1	102.1±8.9	<0.001*	112.9±9.3	103.6±9.3	<0.001*	109.1±11.3	104.5±9.7	0.020*

* P<0.05
ASD: Adjacent segment degeneration
SVA: Sagittal vertical axis
OCI: Occipito-cervical inclination

At baseline, a higher OCI value was significantly correlated to the presence of ASD (OR, 1.05; 95% CI, 1.01-1.09; P=0.009). If patients were dichotomized into mild ASD and ASD, the result was similar (OR, 1.05; 95% CI, 1.00-1.11; P=0.044). C2-C7 lordosis, C2-C7 SVA and T1 slope failed to show a correlation with ASD (Table 5).

At two-year follow-up, again, OCI with higher value was correlated with the presence of ASD (OR, 1.08; 95% CI, 1.04-1.13; P<0.001). If patients were dichotomized into mild ASD and ASD, the correlation between higher OCI and ASD was detected as well (OR, 1.11; 95% CI, 1.06-1.16; P<0.001). Patients with higher OCI value were likewise correlated to the positive progression of ASD (OR, 1.05; 95% CI, 1.01-1.09; P=0.023) (Table 6).

Table 5 Factors associated with presence of adjacent segment degeneration at baseline

Factors	Comparison	non-ASD vs. ASD			mild ASD vs. ASD		
		OR	95% CI	P value	OR	95% CI	P value
Lordosis	Per additional degree	0.99	0.96-1.02	0.566	1.02	0.98-1.06	0.411
SVA	Per additional mm	1.00	0.98-1.02	0.883	1.03	1.00-1.06	0.124
OCI	Per additional degree	1.05	1.01-1.09	0.009*	1.05	1.00-1.11	0.044*
T1 slope	Per additional degree	1.00	0.97-1.04	0.879	1.03	0.99-1.08	0.145

* P<0.05
ASD: Adjacent segment degeneration
OR: Odds ratio
CI: Confidence interval
SVA: Sagittal vertical axis
OCI: Occipito-cervical inclination

Table 6 Factors associated with presence and progression of adjacent segment degeneration at two-year follow-up

Factors	Comparison	non-ASD vs. ASD			mild ASD vs. ASD			ASD negative progression vs. ASD positive progression		
		OR	95% CI	P value	OR	95% CI	P value	OR	95% CI	P value
Lordosis	Per additional degree	0.97	0.94-1.00	0.057	0.97	0.93-1.01	0.133	0.97	0.93-1.01	0.089
SVA	Per additional mm	1.02	0.99-1.05	0.269	1.03	0.99-1.06	0.120	1.01	0.98-1.05	0.421
OCI	Per additional degree	1.08	1.04-1.13	<0.001*	1.11	1.06-1.16	<0.001*	1.05	1.01-1.09	0.023*
T1 slope	Per additional degree	0.99	0.96-1.02	0.490	1.00	0.96-1.04	0.897	0.97	0.93-1.01	0.14

* P<0.05
ASD: Adjacent segment degeneration
OR: Odds ratio
CI: Confidence interval
SVA: Sagittal vertical axis
OCI: Occipito-cervical inclination

As stated above, no significant changes in mean OCI values existed between baseline and two-year follow-up. On an individual level, changes were small for the vast majority of patients, but considerate for a minority of patients (Figure 2). However, no correlation was demonstrated between the change in OCI value and the progression of ASD. Neither was there a correlation between the change in sagittal balance parameter and progression of ASD for the other parameters (Table 7).

Characteristics of clinical outcomes

The clinical outcomes represented by NDI, PCS and MCS were comparable between the three treatment groups, both at baseline and at two-year follow-up (Table 8). Therefore, the clinical outcomes were studied irrespective of surgical methods. At baseline, the mean NDI was 39.7 ± 15.4, mean PCS was 43.3 ± 13.5 and mean MCS was 59.1 ± 21.5. At two years

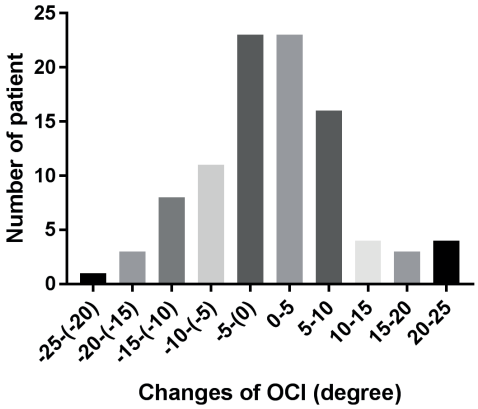

Figure 2 Patient frequency of changes of OCI during two year after surgery

Table 7 The change of sagittal alignment parameter associated with progression of adjacent segment degeneration at two-year follow-up

Association between factors and ASD	Comparison	Univariate analysis		
		OR	95% CI	P value
Lordosis changes	Per additional degree	1.02	0.95-1.08	0.618
SVA changes	Per additional mm	1.01	0.95-1.08	0.711
OCI changes	Per additional degree	1.07	0.99-1.16	0.103
T1 slope changes	Per additional degree	1.02	0.93-1.13	0.618

ASD: Adjacent segment degeneration
OR: Odds ratio
CI: Confidence interval
SVA: Sagittal vertical axis
OCI: Occipito-cervical inclinatio

after surgery, the NDI decreased to 16.4 ± 17.1. PCS and MCS increased to 73.9 ± 23.6 and 77.6 ± 21.8, respectively.

Correlation between cervical sagittal alignment and clinical outcomes

At two-year follow-up, the values of C2-C7 lordosis, C2-C7 SVA, OCI and T1 slope failed to correlate with clinical conditions, and neither was there a correlation of clinical outcome to the changes of these parameters (P>0.05).

Correlation between cervical sagittal alignments

SVA was significantly correlated with T1 slope (0.45-0.54, P<0.01) and OCI (0.20-0.37, P<0.01). C2-C7 lordosis was correlated with T1 slope as well (0.40-0.55, P<0.01) (Table 9).

Table 8 Characteristics of clinical outcome

	NDI	PCS	MCS
Baseline			
ACD	39.1 ± 15.3	42.4 ± 13.3	60.7 ± 20.2
ACDF	38.9 ± 14.2	44.7 ± 12.2	59.7 ± 21.0
ACDA	41.1 ± 16.5	42.9 ± 14.0	57.3 ± 23.2
P value	0.589	0.591	0.639
2-year follow-up			
ACD	16.3 ± 14.4	70.7 ± 23.0	74.4 ± 22.9
ACDF	16.0 ± 16.9	76.7 ± 21.5	81.6 ± 19.2
ACDA	16.9 ± 19.6	73.9 ± 25.8	76.5 ± 22.8
P value	0.963	0.497	0.262

NDI: Neck disability index
PCS: Physical-component summary
MCS: Mental-component summary
ACD: Anterior cervical discectomy
ACDF: Anterior cervical discectomy with fusion
ACDA: Anterior cervical discectomy with arthroplasty

Table 9 Correlation between sagittal alignment parameters

	Lordosis	SVA	T1 Slope	OCI
Baseline				
Lordosis	-	-0.11	0.40**	-0.01
SVA	-	-	0.45**	0.20**
T1 Slope	-	-	-	0.01
OCI	-	-	-	-
1 year				
Lordosis	-	0.03	0.55**	0.05
SVA	-	-	0.54**	0.35**
T1 Slope	-	-	-	0.16*
OCI	-	-	-	-
2 years				
Lordosis	-	0.03	0.53**	0.20*
SVA	-	-	0.53**	0.37**
T1 Slope	-	-	-	0.04
OCI	-	-	-	-

SVA: Sagittal vertical axis
OCI: Occipito-cervical inclinatio*
Correlation is significant at the 0.05 level (2-tailed)
** Correlation is significant at the 0.01 level (2-tailed)

DISCUSSION

Cervical sagittal alignment was demonstrated not to be affected by anterior discectomy at two-years follow-up after surgery. The alleged superiority of maintaining cervical alignment in arthroplasty was not established. The occipito-cervical angle, being crucial in maintaining horizontal gaze, was identified as an important factor associated with radiological ASD.

OCI is a relatively new radiological parameter of the angle between the occiput and the cervical spine proposed by Yoon et al.[6]. In this study, it is first applied to investigate the relationship with radiological ASD and clinical outcomes in patients with cervical disc degeneration. Wu et al.[20] reported before that the occipito-C2 angle was correlated with post-operative ASD in a patient group who underwent occipitoaxial spondylodesis. Theoretically, the occipito-cervical angle is dictated by horizontal gaze, and if this angle is imbalanced, it may well lead to compensation of subaxial cervical curvature, which will eventually lead to accelerated degeneration of the cervical spine[21]. This could explain the strong correlation of OCI with ASD detected in this study.

Remarkably, the OCI angle did not change after surgery, although there was significantly more ASD in patients with a higher OCI. Therefore, the result of this study suggests that accelerated degeneration of the cervical spine is dictated by the OCI angle. Thus, accelerated degeneration of the cervical (subaxial) spine can be predicted if the OCI is known. Ideally, a cut-off point of the OCI would be available. ASD is determined in this study in three ways, and therefore three different values are available: for non-ASD, an angle of 102 to 104 degrees was measured, and for ASD angles, varying between 108 and 113 degrees were observed (Table 4). Future studies are needed to confirm and determine cut-off values. Moreover, long-term follow-up studies are needed to study whether ASD or subaxial degeneration continues during longer follow-up or that it stabilizes.

In the current study, no correlation between clinical outcome and sagittal balance parameters could be demonstrated. The C2-C7 SVA and T1 slope did not change in follow-up of surgery, the C2-C7 lordosis only increased minimally, and they did not demonstrate a correlation with ASD. Therefore, an absence of correlation to the clinical outcome is not surprising. However, previous studies did demonstrate an association between sagittal alignment parameters to the quality of life[1,22]. Tang et al.[23] found that the C2-C7 SVA was negatively correlated with PCS and positively correlated with NDI scores after multilevel cervical posterior fusion. Hyun et al.[24] found that C2-C7 SVA greater than 43.5 mm was corresponded to severe NDI (>25). Nevertheless, Jeon et al.[3] and Kwon et al.[25], who compared similar radiographic parameters with NDI and visual analogue scale, reported that no cervical sagittal alignment parameters were significantly correlated with clinical outcomes after ACDF surgery with three levels and two levels, respectively, which are consistent with our results. It has to be noted though that these authors described different surgical approaches. Tang et al.[23] and Hyun et al.[24] reported on patients with posterior cervical fusion surgery. Jeon et al.[3] and Kwon et al.[25] reported on

multilevel anterior fusion surgery of the cervical spine and demonstrated threshold values for C2-C7 SVA of 40 mm[23] and 43.5 mm[24] in contrast to the values that we reported in the majority of patients (mean value: 20.6-22.5 mm).

A limitation of this study is that we have analysed radiographic parameters with a follow-up of only two years after surgery. In contrast to our results other research groups did demonstrate a lower occurrence of ASD in ACDA compared with ACDF with longer follow-up periods[26-30]. These articles, however, had a high or intermediate risk of bias, and estimates of effect were not sufficiently described. Therefore, the level of evidence that ASD occurs more often in ACDF than in ACDA is low[31]. Moreover, a recent study with low risk of bias demonstrated that the presence of both clinical ASD and radiological ASD was similar in the ACDA and ACDF at five-year follow-up[32]. It is thus debatable whether ASD will demonstrate differences between the three groups upon longer follow-up periods. However, in our opinion, the current data on ASD, demonstrating a gradual increase of ASD in all three groups, makes this rather unlikely.

CONCLUSIONS

The choice of the intervertebral device in anterior cervical discectomy surgery does not influence cervical sagittal alignment. OCI was demonstrated to be an important factor associated with radiological ASD, suggesting that occipito-cervical alignment influences accelerated cervical degeneration. The correlation between cervical sagittal alignment parameters and clinical outcome is absent.

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Chapter 7

Association Between Modic Changes, Disc Degeneration, and Neck Pain in the Cervical Spine: A Systematic Review of Literature

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ABSTRACT

Objective

The objective of this study was to review current literature on the association between Modic changes (MCs), cervical disc degeneration, and neck pain.

Methods

A literature search was performed in PubMed, Embase and Web of Science using a sensitive search string combination. Studies were selected by predefined selection criteria and risk of bias was assessed using a validated Cochrane Checklist adjusted for this purpose.

Results

Fourteen articles that associated MCs with neck pain and/or cervical disc degeneration were included in the present study. Ten articles showed low risk of bias and four showed intermediate risk of bias. The prevalence of MCs in cervical spine varied from 5 to 40% and type II was predominant. Patients with MCs were reported to experience more neck pain and disability. Cervical disc degeneration was detected more frequently in patients with MCs.

Conclusions

MCs were found to be associated with neck pain and with disc degeneration. Therefore, the large variation in prevalence that is reported is highly dependent on the nature of the studied population.

INTRODUCTION

Peridiscal bone marrow changes in vertebral bodies can be visualized by magnetic resonance imaging (MRI) and are generally referred to as Modic changes (MCs) or vertebral endplate signal changes (VESC). In 1988, Modic et al.[1,2] described three types of signal changes in the bone marrow adjacent to the vertebral end plates. Type I lesions, hypointense on T1-weighted imaging (T1WI) and hyperintense on T2-weighted imaging (T2WI), represent marrow edema, and are associated with inflammatory changes in the vertebral endplates. Type II lesions, hyperintense signal on T1WI and hyperintense signal on T2WI, represent bone marrow ischemia with conversion of normal red hematopoietic bone marrow to yellow fatty marrow. Type III lesions, hypointense both on T1WI and T2WI, are considered to represent sclerotic changes of the endplates.

MCs, particularly type I, are believed to be associated with accelerated degenerative changes in the vertebral column[3]. It is therefore interesting to explore whether these MCs are associated with degenerative signs of the intervertebral disc or with clinical implications of degenerative changes. For evaluating intervertebral disc degeneration, several evaluation systems exist[4,5] of which the MRI Pfirrmann grading system is the most commonly used[6]. To evaluate the clinical implication of spine, degeneration pain (low back pain or neck pain), or loss of functionality are usually scored.

Although several studies have evaluated the role of MCs in relation to spinal pain, most of them concentrated on low back pain[7-9]. It would be interesting to evaluate the correlation in the cervical spine. Some studies have reported an association between cervical disc degeneration and neck pain[10,11] but literature on the association between MCs and neck pain in the cervical spine is scarce[5].

To the best of the authors' knowledge, there is no review discussing the association between cervical MCs, disc degeneration, and clinical symptoms. This literature review aims to shed a light on this relationship.

METHODS

The systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement[12].

Search strategy and study selection

In December 2016, the electronic databases PubMed, Embase, and Web of Science were searched using the search strategies (complete search strategies can be found in the Figure 1). To maintain inter-rater reliability, two of the authors (XY and DK) independently screened the articles by title, abstract or by full article, when necessary, to select the studies that met

the predefined selection criteria. Reference screening and citation tracking were performed on the identified articles and as a final check, the reviews found in the first search were studied to make sure no relevant articles were missed. Moreover, supplementary literature searches were performed from December 2016 to September 2017 and from September 2017 to September 2019 aiming to find recent articles.

Neck pain (performed 24.11.2016, 15.09.2017 and 17.09.2019)

PUBMED (417+24+167 results)
(MODIC[all fields] OR "Intervertebral Disc Degeneration"[majr] OR "Intervertebral Disc Degeneration"[ti] OR "Intervertebral Disc Degenerations"[ti] OR "Intervertebral Disk Degeneration"[ti] OR "Intervertebral Disk Degenerations"[ti] OR vesc[all fields]) AND (Neck[ti] OR cervical*[ti] OR cervix[ti] OR NDI[ti] OR VAS[ti] OR NRS[ti])
WEB OF SCIENCE (25+8+3 results)
(TS=(MODIC OR vesc) OR TI=("Intervertebral Disc Degeneration*" OR "Intervertebral Disk Degeneration*")) AND TI=(Neck OR cervical* OR cervix OR NDI OR VAS OR NRS)
EMBASE (437+5+35 results)
(MODIC.mp. OR exp *intervertebral disk degeneration/ OR "Intervertebral Disc Degeneration*".ti. OR "Intervertebral Disk Degeneration*".ti. OR vesc.mp.) AND (Neck.ti. OR cervical*.ti. OR cervix.ti. OR NDI.ti. OR VAS.ti. OR NRS.ti.)

Disc degeneration (performed 30.11.2016, 15.09.2017 and 17.09.2019)

PUBMED (130+37+57 results)
((MODIC[all fields] OR vesc[all fields]) AND cervic*[all fields] AND (disc[all fields] OR discs[all fields] OR disk[all fields] OR disks[all fields])) OR (cervic*[ti] AND (disc[ti] OR discs[ti] OR disk[ti] OR disks[ti]) AND ("Intervertebral Disc Degeneration/diagnosis"[Majr] OR "Intervertebral Disc Degeneration/pathology"[Majr] OR "Intervertebral Disc Degeneration/radiography"[Majr] OR "Intervertebral Disc Degeneration"[ti] OR "Intervertebral Disc Degenerations"[ti] OR "Intervertebral Disk Degeneration"[ti] OR "Intervertebral Disk Degenerations"[ti])) OR ((cervic*[ti] AND (disc[ti] OR discs[ti] OR disk[ti] OR disks[ti]) AND (degenerate*[ti] OR hernia*[ti]) NOT surgery[ti] NOT surgic*[ti] NOT medline[sb])

WEB OF SCIENCE (37+15+6 results)
(TS=(MODIC OR vesc) AND TS=cervic* AND TS=(disc* OR disk*)) OR (TI=cervic* AND TI=(disc* OR disk*) AND TI=Intervertebral AND TI=Degeneration*) NOT TI=surgery NOT TI=surgic*)

EMBASE (133+3+17 results)
((MODIC.mp. OR vesc.mp.) AND cervic*.mp. AND (disc*.mp. OR disk*.mp.)) OR (cervic*.mp. AND (disc*.ti. OR disk*.ti.) AND (exp *intervertebral disk degeneration/di OR "Intervertebral Disc Degeneration*".ti. OR "Intervertebral Disk Degeneration*".ti.)) NOT surgery.ti. NOT surgic*.ti.)

Figure 1 Search strategy

Inclusion criteria

Included were articles that reported the correlation between MCs occurring in the cervical spine with clinical outcomes (assessed by Neck Disability Index (NDI), Numeric Rating Scale (NRS) neck pain, or Visual Analogue Scoring (VAS) for neck pain) and/or cervical disc degeneration. The article had to be published in English in a peer-reviewed journal.

Exclusion criteria

Reviews, meta-analyses, animal studies and case reports were excluded.

Any discrepancy in selection between the two reviewers was resolved in an open discussion with a third reviewer (CVL).

Evaluation of risk of bias

The methodological quality of these studies was assessed by two independent reviewers (XY and DK), using an adjusted version of the checklist for cohort studies of the Dutch Cochrane Centre[13]. When there was no consensus about the assessment, a third reviewer (CVL) was consulted.

The items reviewed in the assessment were: well-defined patient group and study goal, selection bias, and outcome bias. Well-defined patient group and study goal: a maximum of three points could be assigned: one point for clear study objective and inclusion criteria, one point for a clear definition of MCs, and one point for detailed information on patient demographics. Selection bias being absent was assigned one additional point. Outcome bias could be assigned with a maximum of three points: one point if outcome was defined properly, an additional point for the presence of a scoring classification, and one point for the combination of a valid statistical analysis, an independent radiological evaluation (blinded to clinical results), and independence of investigators. Studies could be awarded a maximum of seven points indicating the lowest risk of bias. Studies were divided into a low (six-seven points), intermediate (four-five) or high (three or less points) risk of bias group using a method adapted from Furlan et al.[14].

Definition of Modic changes

In order to accurately judge MCs, we made an inventory of all different methods used in the gathered articles to grade MCs. Usually, MCs were scored by different types of bone marrow changes into type I (hypointense on T1WI and hyperintense on T2WI), type II (hyperintense on T1WI and isointense or hyperintense T2WI) and type III (hypointense on both T1WI and T2WI), based on the definition made by Modic et al.[2] in 1988. Miller[15] made a slight adjustment to this classification by adding a grade 0, meaning no MCs present. Another addition was made in the classification proposed by Weishaupt et al., focusing on the degree to which MCs are present. MCs according to Weishaupt et al.[16] are classified in four categories: *normal*, no abnormality in T1WI or T2WI; *mild*, the scope of signal intensity change equals or is less than 25% of the vertebral height; *moderate*, the signal changes occupy between 25% and 50% of vertebral height; *severe*, the signal changes are equal to or are more than 50% of vertebral height.

Definition of disc degeneration

In order to grade disc degeneration, several grading systems exist. We scored grading systems that were used in the assembled articles. The most frequently used score system is the Pfirrmann grading[6], which classified disc degeneration into five grades based on the T2WI. Other articles that were retrieved described additional scoring systems. According to the location category, the type of classification related to disc degeneration were identified into no disc degeneration, disc bulging, disc protrusion, disc extrusion and disc sequestration by Fardon

et al.[17]. Sive et al.[18] scored disc degeneration from 0 to 12 via different histologic features. Additionally, Griffith et al.[19] and Miyazaki et al.[20] scoring systems are upgraded scoring systems with higher resolution and derived from Pfirrmann grading system. According to Goffin scoring system, disc degeneration was defined based on the loss of disc height and the presence and size of anterior osteophyte formation on x-ray[21]. Matsumoto et al.[22] evaluated disc degeneration according to four features: decrease in signal intensity of intervertebral discs, posterior disc protrusion, disc space narrowing and foraminal stenosis.

Definition of neck disability

To evaluate clinical outcome, different patient-reported outcome measures were used. The NDI is a modification of the Oswestry Low Back Pain Index and has been shown to be reliable and valid for patients with cervical pathology[23-25]. Additionally, NRS and VAS were used for patient-reported neck pain intensity.

Data extraction

Information was independently extracted by two reviewers (XY and DK). Data on study design, sample size, mean age, and sex were collected. With regard to outcomes, the prevalence and the type of MCs (I, II or III) in cervical spine, the prevalence and grading of disc degeneration, and the neck disability score were collected. All articles reported either on the relationship of MCs and neck pain or the relationship of MCs and cervical disc degeneration.

RESULTS

Characteristics of studies and risk of bias

A total of 1,556 articles were identified, of which 1,000 original articles were left after removing duplicates. Titles and abstracts were screened, resulting in 23 eligible articles. After reading full-text articles in total, 14 studies met all criteria to compare MCs with neck pain and/or cervical disc degeneration (Figure 2): seven of those articles discussed the relationship of MCs with both neck pain and disc degeneration[5,26-31]. Three articles evaluated the relationship of MCs with neck pain[32-34] and the other four studies correlated cervical disc degeneration to MCs[4,35-37].

Study characteristics are demonstrated in Table 1 and 2. A total of 5,252 patients were included, with a sample size varying from 44 to 1,520.

Risk of bias

Ten[4,5,27,28,30,31,33,35-37] studies were assessed to have a low risk of bias, meanwhile, and four studies[26,29,32,34] showed an intermediate risk of bias. In five of 14 studies[4,27,28,33,35], selection bias was absent (Table 3).

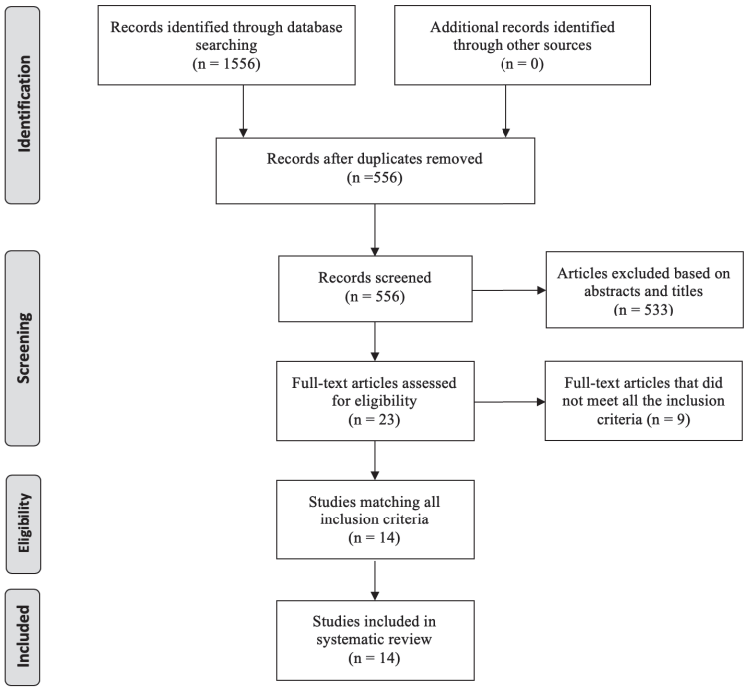

Figure 2 Flow diagram

Reliability of the classification system

Reliability of MCs classification was evaluated by calculating Cohen's Kappa statistics[38,39], and 11 studies provided the results for either or both interobserver and intraobserver reliability. Regarding intraobserver reliability on MCs classification, nine studies[5,26,27,29-31,33,35,36] reported κ values and values varied from 0.64 to 0.89, indicating substantial to excellent reliability. All 11 studies[4,5,26,27,29-33,35,36] reported κ values on interobserver reliability. Nine studies showed substantial to excellent reliability (0.62-0.89). One study reported a κ value of 0.11 (poor reliability)[31] and another one reported a κ value of 0.54 (moderate reliability)[36] (Table 4).

Prevalence of Modic changes

The prevalence of MCs in the cervical spine varied from 5% to 40%. Type II was predominant in the cervical spine and type III was the least prevalent. The prevalence of type I MCs varied from 1.8% to 14.8%, and type II from 1.4% to 33.2% (Table 1). Additionally, eight studies[5,26-30,35,37] that specifically reported the finding of MCs at the specific levels most frequently identified MCs to be present at C5-6.

Table 1 Characteristics of studies-patients with Modic changes

Study (year of publication)	Risk of bias		Type of study	Population	Mean age (years)	N of patient	N of patient with MCs	Type I	Type II	Type III
An (2017)	7*		Retrospective	Patients with cervical kyphosis	54.2 ± 12.2	286	102 (35.6%)	NA	NA	NA
Davies (2016)	7*		Prospective	Patients after cervical discectomy surgery for radicular pain	51 ± 11	90	NA	NA	NA	NA
Hayashi (2014)	7*		Prospective	Patients with neck pain	49.8 ± 10.0	437	84 (19.2%)	NA	NA	NA
Kang (2017)	6*		Retrospective	patients with one-level cervical degenerative diseases	50.7 ± 10.3	169	66 (39.1%)	3 (1.78%)	56 (33.14%)	7 (4.14%)
Kressig (2016)	**5***		Prospective	Patients with cervical disc herniation and neck pain	**44.73 ± 7.9**	**44**	**13 (29.5%)**	**NA**	**NA**	**NA**
Li, S-Y (2014)	6*		Retrospective	Patients with neck pain	44.9 ± 11.1	1520	132 (8.7%)	NA	NA	NA
Li (2017)	7*		Retrospective	Patients with or without nonspecific axial neck pain	50.9 ± 12.6	604	266 (44%)	65 (10.8%)	189 (31.3%)	12 (2.0%)
Mann (2011)	6*		Retrospective	Patients over the age of 50 with neck pain	61.7 ± 9.12	426	172 (40.4%)	63 (14.8%)	121 (28.4%)	0
Matsumoto (2012)	**5***		Prospective	asymptomatic healthy volunteers	**50.5**	**223**	**10 (4.5%)**	**7 (3.1%)**	**3 (1.4%)**	**0**
Average	-				50.0	375	-	-	-	-
Follow-up										
Kressig (2016)	5*	1y	Prospective	Patients with cervical disc herniation and neck pain	44.73 ± 7.9	40	11 (27.5%)	NA	NA	NA
Matsumoto (2012)	5*	11.6y	Prospective	asymptomatic healthy volunteers	38.9	223	31 (13.9%)	10 (4.5%) #	19 (8.5%) #	2 (0.9%)

NA: Not available
N: Number
MCs: Modic changes
#: 2 mixed type (MCs type I and II) was assigned to two groups

Table 2 Characteristics of studies-segments with Modic changes

Study (year of publication)	Risk of bias	Mean age (years)	N of segment	N of segment with MCs	Type I	Type II	Type III
An (2017)	7*	54.2±12.2	1430	113 (7.9%)	38 (2.7%)	75 (5.2%)	0
Davies (2016)	7*	51±11	106	42 (40%)	15 (14.2%)	22 (20.8%)	5 (4.7%)
Hayashi (2014)	7*	49.8±10.0	2185	109 (5.0%)	27 (1.2%)	72 (3.3%)	10 (0.5%)
Kang (2017)	6*	50.7±10.3	NA	NA	NA	NA	NA
Kressig (2016)	**5***	**44.73±7.9**	**NA**	**NA**	**NA**	**NA**	**NA**
Li, S-Y (2014)	6*	44.9±11.1	6138	108 (1.8%)	35 (0.6%)	70 (1.1%)	3 (0.05%)
Li (2017)	7*	50.9±12.6	1330	275 (20.7%)	70 (5.3%)	175 (13.2%)	12 (0.9%)
Mann (2011)	6*	61.7±9.12	1704	245 (14.4%)	74 (4.3%)	171 (10%)	0
Matsumoto (2012)	**5***	**50.5**	**1338**	**10 (0.7%)**	**7 (0.5%)**	**3 (0.2%)**	**0**
Average	-	50	1786	-	-	-	-
Follow-up							
Kressig (2016)	5* 1y	44.73±7.9	NA	NA	NA	NA	NA
Matsumoto (2012)	5* 11.6y	38.9	1297	41 (3.2%)	13 (1.0%)	25 (1.9%)	3 (0.2%)

NA: Not available
N: Number
MCs: Modic changes

Table 3 Risk of bias

Study (year of publication)	Risk of bias scale (7)	Well-defined patient group and study goal (3)	Properly outcome examined (3)	Absence of selection bias (1)	Risk of bias
An (2017)	*6**	***	**	*	Low
Davies (2016)	7*	***	***	*	Low
Hayashi (2014)	7*	***	***	*	Low
Kang (2017)	*6**	***	***	-	Low
Kressig (2016)	5*	**	***	-	Medium
Li, S-Y (2014)	6*	***	***	-	Low
Li (2017)	*7**	***	***	*	Low
Mann (2011)	6*	***	***	-	Low
Matsumoto (2012)	5*	**	***	-	Medium

Modic changes and neck pain

Three articles studied this. An et al.[33] studied patients with kyphosis. They included 283 patients of which circa half had neck pain (no scoring). They evaluated the presence of MCs (1/3 of patients) and demonstrated that MCs were associated with axial neck pain (odd ratio [OR] 5.356; 95% confidence interval [CI] 1.314-12.8; P<0.001). Kressig et al.[32] evaluated neck disability and neck pain in patients with a herniated disc. MCs were demonstrated in one-third of patients. The median NDI score in patients with MCs was 23 and higher than

the median NDI of 15 reported by those without MCs (P=0.04). Neck pain in patients with MCs was also higher (NRS 7) in comparison to patients without MCs (NRS 5.5), though this difference was not significant (P=0.08). Zhou et al.[34] included 117 patients who underwent anterior cervical discectomy and fusion, of which 24% of the patients were found to have MCs. They demonstrated that preoperative MCs adjacent to the operated vertebral body is a risk factor for developing postoperative axial symptoms (shoulder and neck pain, VAS neck pain) (OR 3.268, 95% CI 1.255-8.511, P=0.015).

Table 4 Inter- and intra-observer agreement

Study	Risk of bias	Intra-observer	Inter-observer
An (2017)	7*	0.81	0.72
Davies (2016)	7*	-	0.8
Hayashi (2014)	7*	0.74	0.78
Kang (2017)	6*	-	-
Kressig (2016)	5*	-	0.86
Li (2014)	6*	0.74-0.89	0.74-0.89
Li (2017)	7*	0.81	0.73
Mann (2011)	6*	0.82 (95% CI=0.72-0.92)	0.54 (95% CI=0.43-0.65)
Matsumoto (2012)	5*	0.64	0.62

Modic changes and disc degeneration

This was studied in four articles. Hayashi et al.[35] studied 437 patients that all suffered from neck pain, and MCs were detected in one-fifth of patients. It was shown that subjects with MCs were more likely to have severe disc degeneration (Miyazaki system, defined as over grade IV) at the same segmental level (OR 3.9, 95% CI 2.42-6.3) compared with those without MCs. Mann et al.[36] investigated 426 patients over the age of 50 and circa 40% of patients were found to have MCs. The risk ratio that compared the presence of MCs with disc extrusion at the same level was reported as 2.42 with 95% CI 1.93 to 3.04, suggesting patients with MCs are nearly 2.5 times more likely to have a disc herniation compared with patients without MCs. Kang et al.[37] studied 169 patients with neck pain, of which 30% had MCs, and those with MCs had a more aggravated grade of disc herniation (Matsumoto system; P<0.01). Davies et al.[4] studied 90 patients who underwent cervical discectomy surgery for radicular pain, and evaluated disc degeneration by means of radiological (Miyazaki system) and histological (Sive system) classification systems. In this study, circa 40% of patients were detected to have MCs, and no correlation was found for MCs compared with MRI grades of degeneration (Spearman Rho: 0.17, P=0.07) nor with histological grades (Spearman Rho=0.11, P=0.3, Table 5)

Table 5 Modic changes with cervical disc degeneration

Study (year of publication)	Risk of bias	Classification of degeneration	Prevalence of disc degeneration
Davies (2016)	7*	Miyazaki system (MRI) and Sive system (Histology)	Miyazaki system: Grade II: 2%; Grade III: 35%; Grade IV: 58%; Grade V: 5% Sive system: Mild (0-IV): 7%; Moderate (V-VIII): 59%; Severe (IX-XII): 34%
Hayashi (2014)	7*	Miyazaki system	Mild (I-III): 56.1% Severe (IV-V): 43.9%
Kang (2017)	*6**	Motsumoto system	Grade I: 26.5% Grade II: 37.9% Grade III: 25.6% Grade IV: 10%
Li, S-Y (2014)	6*	Pfirrmann system	Grade I: 8.3% Grade II: 27.5% Grade III: 59.4% Grade IV: 4.6% Grade V: 0.1%
Li (2017)	*7**	Schneiderman system	NA
Mann (2011)	6*	Type 1- disc bulge; Type 2-disc protrusion, herniation and extrusion	Type I: 13.3% Type II: 28.9%
Matsumoto (2012)	5*	1. Decreased signal intensity of the intervertebral discs; 2. Posterior disc protrusion; 3. Disc space narrowing; 4. Foraminal stenosis	The percentage with positive findings: 1: 29.4% 2: 20.1% 3. 6.5% 4. 2.7%

Modic changes with both neck pain and disc degeneration

This combination was studied in seven articles. Li et al.[5] studied 1,520 patients with neck pain, and 9% of patients were detected to have MCs. The prevalence of MCs was higher in patients with neck pain (no scoring system) (8.7% versus 3.3%, P=0.00). Furthermore, the prevalence of MCs increased with grade of cervical disc degeneration (Pfirrmann system; Spearman rank 0.220, P=0.000).

Matsumoto et al.[26] studied 497 asymptomatic patients and found that the association of development of MCs through 10 years follow-up was positively correlated with several indicators of progression of disc degeneration: posterior disc protrusion (OR 2.6, 95% CI 1.1-6.0), disc space narrowing (OR 4.2, 95% CI 1.9-9.5), and foraminal stenosis (OR 4.2, 95% CI 1.5-1.16). There was no association between MCs and neck pain (no scoring system) at the end of follow-up (P=0.16).

Li et al.[27] studied asymptomatic and symptomatic patients that consecutively visited the outpatient clinic with varying neck problems. A total of 266 patients with MCs were

compared with 338 patients without MCs. It was demonstrated that the patient group with MCs had more patients with axial neck pain (42.1% versus 26.6%, P=0.000) and higher disc degeneration score (Schneiderman system) compared to those without MCs (4.6 ± 2.8 versus 2.2 ± 2.5, P=0.032).

Kong et al.[31] studied 381 patients with cervical radiculopathy or myelopathy, and 47 of them had MCs. They demonstrated that MCs were not correlated with severe neck pain (defined as at least five points on the NRS), but MCs were found to be a predictive factor correlated with persistent neck pain (defined as at three points on the NRS for more than 12 months) (OR 2.308 95% CI 1.244-4.282, P<0.05). It was also demonstrated that severe disc degeneration (defined as over grade IV in Pfirrmann system) was associated with MCs (OR 2.423, 95% CI 1.169-5.023, P<0.05).

Qiao et al.[29] studied 539 patients who suffered from cervical spondylotic myelopathy, and 13% of them showed MCs. It was demonstrated that the presence of MCs was correlated with durations of axial symptoms (shoulder and neck pain, no scoring system) more than 18 months (X^2=23.438, P=0.000). This study also reported that a higher prevalence of MCs was found in patients with high grade of degenerative discs (defined as over grade III in Pfirrmann system, X^2=223.137, P=0.000).

Tsuji et al.[30] reported the finding of MCs with 20-year follow-up, of which the result of 10-year follow-up was reported by Matsumoto et al.[26]. A total of 193 patients were included in this study and 16% of patients were found to have MCs. Unlike with the result of 10-year follow-up, neck pain (no scoring system) was associated with the presence of MCs in this follow-up (OR 2.71, 95% CI 1.08-6.80, P=0.033). They also demonstrated that pre-existing posterior disc protrusions were associated with the development of MCs (OR 3.31, 95% CI 1.21-9.05, P=0.020).

Yang et al.[28] studied 223 patients with radiculopathy derived from two RCTs and reported the MCs findings both at baseline (18%) and at one-year follow-up (23%). They reported that there was no correlation between MCs and neck pain (scored by NDI neck pain intensity section and VAS neck pain), neither at baseline nor at one-year follow-up. However, they found that cervical disc degeneration (Goffin system) was correlated with the presence of MCs (OR 2.40, 95% CI 1.171-4.938) preoperatively, but this correlation disappeared at one year after surgery.

Conversion of Modic changes

Matsumoto at al.[26] studied MCs in asymptomatic patients during an average follow-up period of 11.6 years. Forty-one (3.2%) intervertebral levels were detected to be with MCs at follow-up compared with ten subjects (0.8%) in baseline. Of the 13 segments with MCs type I in follow-up, ten were newly developed, two remained as type I and one changed from type II to type I. Of 25 type II intervertebral segments, 22 were newly developed, one changed from type I to type II, and two remained as type II. All three type III segments at follow-up were

newly appeared. Four type I segments in the previous study had returned to normal at follow-up. Yang et al.[28] reported the conversion of MCs preoperatively and one year postoperatively. At one-year follow-up, they demonstrated that 13 MCs type II levels consisted of 11 newly developed and two maintained as type II. Of eight levels with MCs type I, seven were newly developed and one maintained as type I.

Modic changes and age

The mean age of patients in the included studies is 50.9 years with a range of 44.7 to 61.7 years. Seven studies[4,5,26,28-30,32] correlated age to the presence of MCs. Li et al.[5] reported that MCs significantly occurred more often in patients with older age in a 1,520 patient group with an age range of 19-86 years (spearman rank correlation: 0.217, P=0.000). Similarly, another study[26] demonstrated that age ≥40 years was a significant factor associated with the development of new MCs (OR 8.0, 95% CI 2.7-23.3, P=0.01) (223 patients, range of age 23-83). Qiao et al.[29] also showed that MCs tend to occur in patients over 40 years of age in a 539 patient group with an age of range 24 to 87 years (X^2=57.437, P=0.000).

Two much smaller studies could not demonstrate a correlation between age and MCs (Kressig et al.[32], 44 patients, P=0.099; Davies et al.[4], 90 patients, P=0.8). Similarly, another two studies with a group of circa 200 patients could not confirm this relationship neither: Yang et al.[28] (223 patients) and Tsuji et al.[30] (193 patients) did not found the correlation between age and the presence of MCs.

DISCUSSION

MCs in the cervical spine vertebrae are positively associated with the prevalence of neck pain and with the prevalence of disc degeneration. The huge variation of the presence of MCs that is reported in literature (5% to 40%) is highly dependent on the patient population studied. The lower part of the spectrum (5%) comes from a study in a group of asymptomatic volunteers, and the higher end of the spectrum (40%) is reported in a population with neck pain.

All the studies demonstrate that MCs type II are predominant in the cervical spine and that C5-6 is the most frequent level (and C6-7 the second most frequent level) at which MCs are diagnosed. As the endplates of C5-C7 sustain more weight than the higher levels and vertebrae are less limited in their excursion, greater momentum on the vertebral endplates are transmitted.

With a high quality of evidence, disc degeneration was positively correlated with MCs in the cervical spine, suggesting that the patients with MCs have more severe cervical disc degeneration. The only result of noncorrelation was described by Davies et al.[4] that only studied a small number of discs (106 discs) in comparison to the other studies (studying 256

to 6,138 discs). However, this is the only study using a histologic method to evaluate disc degeneration. Since histologic evaluation of intervertebral disc tissue is deemed the most accurate and sensitive method of identifying disc degeneration[40,41], more studies are needed to clarify the correlation between cervical disc degeneration assessed by histologic methods and MCs.

A significant association of MCs with age was demonstrated in two large studies (Li et al.[5] and Matsumoto et al.[26]). This association is confirmed by results of a study from de Bruin et al.[42] that showed an extremely low percentage (0.3%) of segments with MCs in a young patient group (average age of 30 years). Older patients are more likely to be suffering from disc degeneration, and from the positive association of MCs with disc degeneration, it is only logical that MCs are more often occurring in older. Likewise, patients with disc degeneration are more likely to suffer from neck pain and/or disability, and this correlation is therefore also not surprising. However, this correlation could not be affirmed in another four studies[4,28,30,32].

The correlation between MCs and pain has not been elucidated so convincingly in low back pain. El Barzouhi et al.[7] investigated 263 patients with sciatica of which half of the number of patients had also back pain. They demonstrated that disabling back pain was found in nearly the same proportion in patients with and without MCs. This group of patients however was suffering from recent onset sciatica and therefore results may be different than studies in groups of patients with longer lasting complaints, as in the cervical studies gathered in this review on cervical spine. A recent study on patients with long-term pain or disability did however also not demonstrate an association: Udby et al.[43] studied 170 subjects and concluded that MCs were not found to be associated with long-term pain or disability. A meta-analysis performed by Herlin et al.[44] indicated that the associations between MCs and low back pain-related outcomes were inconsistent because of the high risk of bias and the heterogeneity of studies. In agreement with our results though, Zhang et al.[45] and Jensen et al.[46] performed systematic reviews and reported that MCs were correlated to discogenic low back pain. In conclusion, both in neck and in low back pain correlations between pain and MCs have been demonstrated, but the results in the cervical spine are more convincing than those in the lumbar spine.

As we only included studies published in English, those articles reported in other languages were possible omissions, which is a limitation to the incomplete retrieval of identified study.

CONCLUSIONS

MCs are associated with more disc degeneration. Disc degeneration is highly likely to cause neck pain and disability. It is therefore not surprising that neck pain and disability is indeed positively associated with the presence of MCs.

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Chapter 8

Are Modic Vertebral Endplate Signal Changes Associated with Degeneration or Clinical Outcomes in the Cervical Spine?

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ABSTRACT

Objective

To report on the incidence of Modic changes (MCs) in patients with cervical radiculopathy due to a herniated disc. Presence of MCs was correlated to clinical outcomes and the presence of radiological degeneration.

Methods

Patients who underwent anterior discectomy for a cervical radiculopathy due to a herniated disc were analysed for the presence of MCs at baseline and at one-year follow-up after surgery. Neck disability index, physical component summary, mental component summary and visual analogue scale for neck pain and for arm pain were evaluated as clinical outcomes. The presence of radiological degeneration was defined by the method of Goffin.

Results

The prevalence of MCs was found at 18% at baseline and increased to 28% one year after surgery. Both at baseline and at one-year follow-up, the percentage of patients with and without MCs reporting neck pain was comparable. Likewise, both at baseline and at one-year follow-up, the percentage of patients with and without MCs reporting disabling arm pain was comparable. At baseline, the patients with MCs demonstrated more radiological degeneration than those without MCs (OR 2.40), but this difference disappeared at one year after surgery.

Conclusions

MCs were not associated with neck pain, nor with arm pain. Furthermore, there was a tendency for a correlation between the presence of MCs and radiological degeneration.

INTRODUCTION

Cervical radiculopathy is a frequently occurring problem with an annual incidence of about 80 per 100,000 people and a prevalence of 35 per 10,000 inhabitants[1,2]. Another recent study demonstrated an incidence of 1.79 per 1,000 person-years from 2000 to 2009[3]. Patients with cervical radiculopathy present with arm pain in a dermatomal pattern. Magnetic resonance imaging (MRI) of the cervical spine of these patients often demonstrates a bulging or herniated disc compressing the corresponding nerve root.

Frequently, additional neck pain is present. It is usually presumed that neck pain is multifactorial. One of the factors causing neck pain is deemed to be due to the muscle tension due to the continuous contraction of the muscles in response to the radicular pain. Since the spinal nerve root is specifically irritated on movements of the spinal column that narrow the neuroforamen, muscles are under constant tension to prevent these movements. Furthermore, neck pain can be due to general degenerative changes in the cervical spine that accompany the degeneration of the bulging or herniated disc[4]. However, changes in the endplates of the cervical spine, diagnosed as Modic changes (MCs) in the cervical vertebrae, also may be correlated to neck pain because these are associated with degeneration, inflammatory changes and bone marrow ischemia.

MCs or vertebral endplate signal changes can be visualized by MRI. In 1988, Modic et al.[5,6] described three types of signal changes in the bone marrow adjacent to the vertebral endplate. Type I lesions, hypointense on T1 weighted imaging (WI) and hyperintense on T2WI, represent marrow edema, and are associated with inflammatory changes and an acute process in the vertebral end-plate[5,7,8]. Type II lesions are the most common type and are associated with a chronic process, which increase signal on T1WI and isointense or slightly hyperintense signal on T2WI, and represent bone marrow ischemia with conversion of normal red hematopoietic bone marrow to yellow fatty marrow[5,9]. Type III lesions, hypointense both on T1WI and T2WI, are considered to represent sclerotic changes of the endplate[5,10]. Studies on the prevalence of cervical MCs are limited and incidences reported vary considerably ranging from 4.5% to 58%[11,12].

It is interesting to examine the association between MCs and cervical spine degeneration. Radiological signs of degeneration of the cervical spine can be scored on x-rays by the score of Goffin et al.[13], which was designed to score adjacent level degeneration in the cervical spine. There are, however, indications that spine degeneration is increased in by demographic factors[14]. The possible confounding factors will be examined.

It is furthermore interesting to explore whether MCs are associated with clinical parameters representing neck pain. Moreover, MCs have been reported to represent the inflammatory status of the vertebral body and the adjacent disc. This is hypothesized to influence the spinal root and thus influence pain in the arm[15,16]. Therefore, the correlation between MCs and arm pain also will be investigated.

For these research questions, we combined the data of two randomized double-blind trials, performed in the Netherlands, on patients treated by anterior cervical discectomy with or without interbody fusion and arthroplasty for cervical radiculopathy with a similar setup. The objective of this study is to investigate the prevalence of MCs in the cervical spine and its association to radiological degeneration and to correlate MCs to neck and arm pain.

METHODS

Study design

NECK trial

A prospective, randomized double-blind multicentre trial among patients with cervical radiculopathy due to single-level disc herniation was conducted. Patients randomly were assigned into three groups: anterior cervical discectomy with arthroplasty (ACDA; activC, Aesculap AG, Tuttlingen, Germany), anterior cervical discectomy with fusion (ACDF; Cage standalone) and anterior cervical discectomy without fusion (ACD). A randomized design with variable block sizes was used, with allocations stratified according to centre. All patients gave informed consent.

The design and study protocol were published previously[17]. The two-year follow-up data revealed no differences in clinical outcomes nor in disc or adjacent segment degeneration diagnosed on x-rays and MRI[18].

PROCON trial

The trial design was a prospective, double blind, single-centre randomized study, with a three-arm parallel group. Patients were randomly allocated into three groups: ACDA (Bryan disc prosthesis, Sofamor Danek, Kerkrade, the Netherlands), ACDF (Cage standalone, DePuy Spine, Johnson and Johnson, Amersfoort, the Netherlands), and ACD.

The design and study protocol were published previously[19]. The follow-up data up to eight years post-surgery revealed no differences in clinical outcomes[20] nor in adjacent segment degeneration diagnosed on computed tomography or MRI[21].

Clinical outcomes

Neck disability index (NDI) is a 10-item questionnaire on three different aspects: pain intensity, daily work-related activities and nonwork-related activities. Each item is scored from 0 to 5 and the total score ranges from 0 (best score) to 50 (worst score). This 50 points score was converted to a percentage (50 points=100%). The NDI is a modification of the Oswestry Low Back Pain Index and has been shown to be reliable and valid for patients with cervical pathology[22-24]. To focus on neck pain specifically, additional neck pain was evaluated using the ‘neck pain intensity’ section of NDI questionnaire for all subjects, and disabling neck

pain was defined in the research group consensus meeting as at least 3 points (Table S1). Moreover, physical component summary (PCS) and mental component summary (MCS) were derived from the 36-Item Short Form Health Survey. The PCS and MCS range from 0 to 100, with greater scores representing better self-reported health.

In the NECK trial, patients were additionally assessed by means of the 100-mm visual analogue scale (VAS) for neck pain and for arm pain (with 0 represents no pain and 100 the worst pain ever experienced). Disabling neck pain and arm pain were defined as at least 40 mm since this cut-off value is regularly used when VAS is categorized into favourable and unfavourable outcome[25,26].

Demographic data also were scored for patients and included age, body mass index, sex, smoking, and alcohol use. Alcohol use was defined as no alcohol use and more than occasional drinker. These data were correlated to the presence of MCs and the presence of radiological degeneration at baseline.

Radiological outcomes

All patients underwent MRI at baseline and after one year. MR images were performed at each study centre using a standardized protocol tailored to a 1.5- or 3- Tesla scanner. Standard sagittal T1 and T2 and T2 axial images were obtained, using 3-mm contiguous slices in all directions and an in-plane resolution of 1 mm^2 or less. MCs were defined according to criteria of Modic et al.[5,6].

Standing lateral radiographs of the cervical spine were obtained with the patients in a neutral standing position and instructed to look straight ahead, with hips and knees extended. Radiological degeneration was defined based on the height of the discs and the presence and size of anterior osteophyte formation according to the classification reported by Goffin et al.[13] (Table S2). The radiographs were independently evaluated by one senior neurosurgeon dedicated to spine surgery. The reviewer was not provided with any clinical information of the included patients.

Statistical analysis

After we evaluated radiological degeneration using the method of Goffin et al.[13], subjects who assessed as *normal* for both superior and inferior level were defined as *non-radiological degeneration*, and the patients with either *mild*, *moderate* or *severe* degeneration at either superior or inferior level were defined as '*radiological degeneratio*n'. All the data are presented as mean ± standard deviation. Baseline and follow-up characteristics of the ACD, ACDF and ACDA treatment group were compared using analysis of variance for continuous data and chi-square test for categorical data. Logistic regression analysis was used to determine which factors were associated with the presence of MCs and radiological degeneration at baseline, and the correlation between MCs and radiological degeneration. The comparison on clinical parameters between MCs and non-MCs group was performed by means of the Student's *t*-test

for continuous data; chi-square test or Fisher's exact test were used for categorical data. Tests were two tailed, and a P value of < 0.05 was considered significant. SPSS software, version 23.0, was used for all statistical analyses (SPSS, Inc., Chicago, IL, USA).

RESULTS

In the NECK trial, 111 patients were included and randomly assigned to ACD (38 patients), ACDF (38 patients) or ACDA (35 patients). At baseline, MRI data of 107 patients were available and at one-year follow-up, MRI data were available for 89 patients. X-ray data were available for 107 patients at baseline and for 98 patients at one-year follow-up.

In the PROCON trial, 142 patients were randomized into ACD (45 patients), ACDF (47 patients) or ACDA (50 patients). At baseline, MRI data of 116 subjects were available and at one-year follow-up, MRI data were available for only 31 patients. X-ray data were available for 121 patients at baseline and for 103 patients at one-year follow-up.

Demographics

Baseline characteristics are presented in Table 1. The mean age of the study population was 45.2 ± 7.3 years, ranging from 27 to 70 years. There was no difference regarding to baseline characteristics between treatment groups. Surgery was most frequent at levels C5-C6 and C6-C7.

Table 1 Patient demographics by treatment arm

		ACD	ACDF	ACDA	Total	P value
Population		83	85	85	253	
Age (years, Mean ± SD)		45.3 ± 6.7	45.6 ± 7.6	44.8 ± 7.7	45.2 ± 7.3	0.787
Body Mass Index (Mean ± SD)		26.2 ± 3.8	26.6 ± 4.7	26.7 ± 4.1	26.5 ± 4.2	0.726
Sex	Male	42	37	43	122	0.939
	Female	41	48	42	131	
Smoking	Yes	33	40	41	118	0.305
	No	50	43	44	133	
Alcohol	Yes	46	52	55	153	0.565
	No	37	31	30	98	
Herniated level						
C4-C5		1	2	0	3	
C5-C6		46	39	40	125	
C6-C7		36	43	45	124	
C7-Th1		0	1	0	1	

ACD: Anterior cervical discectomy
ACDF: Anterior cervical discectomy with fusion
ACDA: Anterior cervical discectomy with arthroplasty
SD: Standard deviation

Prevalence of Modic changes

At both baseline and one-year follow-up, there was no difference in the prevalence of MCs between the three treatment arms (total cervical spine: P=0.995 and P=0.190; the index level: P=0.731 and P=0.624, Table S3). Therefore, MCs was studied irrespective of the surgical method applied.

At baseline, MCs was observed in 17.9% of 223 patients: 31 patients had MCs at one level, six patients had MCs at two levels and three-level MCs was found in three patients. Regarding the type of MCs, 4.5% (ten patients) of the patients were found to have type I, 13% (29 patients) had type II and 0.4% (one patients) had both type I and type II. No type III MCs was observed. Focusing on the index level, 3.2% (7 patients) were detected to have type I, and 5.4% (12 patients) had type II MCs (Table 2). Of 1,337 evaluated segments in present study, MCs were observed in 3.9% (52 segments): type I in 0.8% (11 segments) and type II in 3.1% (41 segments) of cervical segments. MCs were the most frequently observed at C5 to C7 (Table S4).

Table 2 Modic changes at the index level

	None	Type I	Type II	Total
Preoperatively				
C4-C5	0	0	1	1
C5-C6	105	4 (3.5%)	5 (4.4%)	114
C6-C7	97	3 (2.8%)	6 (5.7%)	106
C7-Th1	1	0	0	1
Total	203	7 (3.2%)	12 (5.4%)	222
Postoperatively				
C4-C5	0	0	0	0
C5-C6	40	7 (13.2%)	6 (11.3%)	53
C6-C7	30	2 (5.3%)	6 (15.8%)	38
C7-Th1	1	0	0	1
Total	71	9 (9.8%)	12 (13.4%)	92

The number of MRIs available at one-year follow-up was small in the patients from the PROCON trial. At one-year follow-up, MCs was observed in 23.3% of 120 patients: 24 patients had one-level MCs and four patients had two-level MCs. Type II was the predominant type (14.2%, 17 patients). However, in the patients that received a prosthesis, it was not possible to evaluate MCs at the target level, due to scattering on MRI induced by the prosthesis. Therefore, the prevalence of MCs, one year after surgery is underestimated. The figures in Table S3 illustrate this: the percentage of MCs rises to circa 28% at one-year follow-up in the ACD and ACDF groups but decreases in the ACDA group to 13%. Therefore, we did additional analyses on correlations in which we omitted the ACDA results after one year. Focusing on the operated level, one year after surgery, we found that the percentage of seg-

ments with MCs increased to 9.8% (9 segments) for type I and 13.4% (12 segments) for type II, respectively (Table 2), but likewise, this will be underestimated numbers.

Conversion of Modic changes

At one-year follow-up, 13 MCs type II levels consisted of 11 newly developed and two maintained as type II. Of eight levels with MCs type I, seven were newly developed and one maintained as type I (Table 3). Moreover, 11 levels demonstrated MCs at another level than the target level. These data have to be interpreted with caution, since the number of MRIs is low and the index level in the ACDA group could not be evaluated for MCs.

Table 3 Conversion of Modic changes

	Postoperatively			
Preoperatively	None	Type I	Type II	Total
None	0	7	11	18
Type I	0	1	0	1
Type II	0	0	2	2
Total	0	8	13	21

Prevalence of radiological degeneration

There was no difference in the prevalence of radiological degeneration between the three treatment arms, neither at baseline nor at one-year follow-up (Table 4). Therefore, radiological degeneration was studied irrespective of the performed surgical method. At baseline, the prevalence of radiological degeneration was 34% (examined in 228 patients) and it increased to 47% (examined in 201 patients) at one year after surgery.

Table 4 Prevalence of radiological degeneration

	ACD	ACDF	ACDA	P value
Baseline	38% (27)	36% (29)	29% (22)	0.428
1-year follow-up	48% (31)	45% (28)	47% (35)	0.934

ACD: Anterior cervical discectomy
ACDF: Anterior cervical discectomy with fusion
ACDA: Anterior cervical discectomy with arthroplasty

Factors associated with the presence of Modic changes and radiological degeneration at baseline

The presence of MCs at baseline was slightly associated with increasing age (odds ratio [OR], 1.05; 95% confidence interval [CI], 1.00-1.10; P=0.052). Sex, body mass index, smoking, and drinking alcohol failed to reach a statistical association with the presence of MCs (Table 5). Regarding the presence of radiological degeneration, increasing age (OR, 1.12; 95% CI,

1.07-1.18; P<0.001) and alcohol use (OR, 1.82; 95% CI, 1.01-3.30; P=0.047) were found to be factors to be associated with radiological degeneration at baseline (Table 6).

Table 5 Factors associated with presence of Modic changes at baseline

		Univariate analysis		
	Comparison	OR	95% CI	P value
Age	Per additional year of age	1.05	1.00-1.10	0.052
BMI	Per additional unit	1.02	0.94-1.12	0.619
Sex	Male (107) vs. female (111)	0.93	0.47-1.84	0.825
Smoking	Yes (97) vs. no (122)	0.55	0.26-1.12	0.100
Alcohol	Yes (140) vs. no (79)	1.40	0.67-2.93	0.378

BMI: Body mass index
NDI: Neck disability index
OR: Odds ratio
CI: Confidence interval

Table 6 Factors associated with presence of radiological degeneration at baseline

		Univariate analysis		
	Comparison	OR	95% CI	P value
Age	Per additional year of age	1.12	1.07-1.18	<0.001
BMI	Per additional unit	1.02	0.95-1.01	0.534
Sex	Male (111) vs. female (112)	0.77	0.44-1.34	0.768
Smoking	Yes (101) vs. no (123)	0.58	0.33-1.02	0.059
Alcohol	Yes (140) vs. no (84)	1.82	1.01-3.30	0.047

BMI: Body mass index
NDI: Neck disability index
OR: Odds ratio
CI: Confidence interval

Association of Modic changes with clinical outcomes

Disabling neck pain (derived from the NDI score) was present in 61.6% of patients at baseline. There was no association with the presence of MCs: disabling neck pain was present in 70% of the patients with MCs, and in 62% of the patients without MCs (P=0.351). Similar results were found at one year after surgery: the proportion of patients with disabling neck pain in the MCs patients was comparable with that in the non-MCs group (33% versus 32%, P=0.877). After we omitted patients in the ACDA group at one-year follow-up, no association was found either (P=0.300).

Disabling neck pain derived from VAS neck pain was only available for the NECK trial, and was 70.6% at baseline. Disabling neck pain failed to correlate with radiological degeneration at baseline as well as at one-year follow-up (Table 7). Likewise, no correlation could be detected if the patients in the ACDA group at one-year follow-up were excluded (P=0.575).

The values for NDI, PCS and MCS in the patients with MCs were comparable with those in the patients who did not demonstrate MCs. Likewise, at one-year follow-up, these clinical outcome parameters were comparable in the patients with and without MCs (Table 7). The numbers of patients with MCs were too low to meaningfully correlate for type I and type II MCs separately.

In addition, VAS arm pain was studied in patients from the NECK trial. The patients with MCs reported disabling arm pain in comparable proportion with those patients without MCs, both at baseline and at one-year follow-up (Table 7). If only the patients with ACD and ACDF at one-year follow-up were considered, the result was similar (P=0.526).

Table 7 Comparison of Modic changes with clinical outcomes

	VAS neck	VAS arm	NDI	PCS	MCS
Baseline					
MCs	81%	71%	40.7 ± 15.9	43.6 ± 14.1	63.7 ± 19.6
Non- MCs	67%	79%	39.3 ± 15.4	44.0 ± 13.5	58.4 ± 22.0
P value	0.203	0.563	0.603	0.891	0.201
1-year follow-up					
MCs	27%	33%	24.0 ± 20.1	64.9 ± 25.9	70.2 ± 23.1
Non- MCs	24%	19%	17.3 ± 14.3	71.3 ± 20.3	78.0 ± 17.8
P value	1.00	0.293	0.158	0.208	0.081

VAS: Visual analogue scale
NDI: Neck disability index
PCS: Physical-component summary
MCS: Mental-component summary
MCs: Modic changes

Association of Modic changes with radiological degeneration

At baseline, in 73 of 77 patients with radiological degeneration MRI data were available. 51% of 37 patients with MCs were found to have radiological degeneration, which was significantly greater than 31% (out of 177 patients) without MCs (OR, 2.40; 95% CI, 1.171-4.938; P=0.017). At one-year follow-up, MRI data were available for 52 patients with radiological degeneration, and the association disappeared. It was shown that 39% of 26 patients with MCs were demonstrated to have radiological degeneration compared with 52% of 81 patients without MCs (P=0.235). After we excluded patients with ACDA, no association was demonstrated as well (P=0.211) (Table 8).

Considering associations between radiological degeneration and MCs at the index level, at baseline, 42% of 19 patients with MCs were found to have radiological degeneration compared with 34% of 194 patients without MCs (P=0.451). After one year, it was found that 35% of 20 patients with MCs at the index level had radiological degeneration, compared with 46.8% of 62 patients in non-MCs group (P=0.356). With exclusion of patients with ACDA, a similar result was shown (P=0.282) (Table 8).

Table 8 Association of Modic changes with radiological degeneration

Radiological degeneration	Time point	OR	95% CI	P value
Total cervical spine	Baseline	2.40	0.203-0.854	0.017
	1-year follow-up	1.72	0.699-4.248	0.237
	1-year follow-up, without ACDA group	1.98	0.679-5.766	0.211
The index level	Baseline	0.69	0.266-1.806	0.453
	1-year follow-up	1.97	0.665-5.837	0.221
	1-year follow-up, without ACDA group	1.94	0.582-6.443	0.282

OR: Odds ratio
CI: Confidence interval
ACDA: Anterior cervical discectomy with arthroplasty

In addition, it was demonstrated that alcohol was a factor that significantly associated with radiological degeneration. Therefore, this was added to the statistical analysis as a covariate. It was demonstrated that a similar correlation was found between MCs and radiological degeneration (OR, 2.38; 95% CI, 1.144-4.945; P=0.020).

DISCUSSION

In patients with cervical radiculopathy due to a herniated disc, one fifth of patients were detected to have MCs, being predominantly type II. One year after cervical discectomy, the prevalence of MCs increased to circa 30%, and remains predominantly type II. If observing MCs around the level with the bulging cervical disc, 9% of patients had MCs at the target level preoperatively, which increased to 23% at one-year follow-up. MCs is most prevalent in the most frequently operated levels from C5 to C7 at both baseline and follow-up, in accordance with literature[27-29]. Our results on the prevalence of MCs in patients with cervical radiculopathy are in agreement with the results of Kressig et al.[30], who also studied patients with cervical radiculopathy. Kressig et al.[30] reported that 29.5% of patients were found to have MCs and that this was 27.5% at one-year follow-up after undergoing manipulative therapy.

It was hypothesized that MCs were associated with neck pain in the cervical spine. This hypothesis could not be affirmed. Other studies reported, contrary to our results, that neck pain was more prevalent in patients with MCs in the cervical spine[27,31,32]. However, information on the scoring method for neck pain was absent in these papers. In our study, with the use of an accurate and representative measures for neck pain, it was shown both at baseline and at one year after surgery, that patients with and without MCs reported disabling neck pain in a comparable proportion. Our results are in agreement with Matsumoto et al.[11] who demonstrated the absence of a correlation between neck pain and cervical MCs in 223 asymptomatic healthy volunteers.

MCs are hypothesized to represent an inflammatory process involving low virulent anaerobic bacteria[16], which may influence the spinal root and thus influence pain in the arm. The correlation of MCs with disabling arm pain was, however, not confirmed in the present study. This result is consistent with previous research reported by Kressig et al.[30]. El Barzouhi et al.[33] could not demonstrate a correlation between back pain and MCs. But Djuric et al.[15] did find a MCs dependent correlation between back pain/leg pain and the presence of macrophages in disc tissue in patients operated for sciatica due to a herniated disc. Nevertheless, these studies were conducted on data from the lumbar spine, and the value of these findings for the cervical spine remain unclear. Additional research is needed.

Radiological degeneration is present at baseline in one third of patients, and we demonstrated that it tends to be associated with MCs (OR 2.40). The only correlation that was convincing was the correlation between MCs (considering the global cervical spine) and radiological degeneration at baseline. However, since this correlation could not be confirmed in the analysis considering only the target level and disappeared at one year after surgery, we softened the conclusion to 'tending to correlate'. The absence of a correlation at one year after surgery may be due to the lower number of MRIs that were available. A limitation of this study is that MRI studies and x-rays were not available for all patients. Furthermore, it would have led to stronger results if the VAS neck pain was assessed for the patients in the PROCON study, too. Finally, the prosthesis lacks proper evaluation of MCs at the adjacent levels, which lowered the number of patients in which MCs could be studied even more. Future studies are needed to investigate the change of the prevalence of MCs between the pre- and post-operative condition. A large series of such patients is also need in order to compare neck and arm pain as well as radiological degeneration between different types of MCs.

CONCLUSIONS

The prevalence of MCs was found at 18% at baseline and increased to 28% at follow-up. MCs were not correlated to neck pain, but tended to be correlated to radiological degeneration in the cervical spine.

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Table S1 Neck pain intensity

Score	Pain intensity
0	No pain at the moment.
1	The pain is very mild at the moment.
2	The pain is moderate at the moment.
3	The pain is fairly severe at the moment.
4	The pain is very severe at the moment.
5	The pain is the worst imaginable at the moment.

Table S2 The classification of radiological degeneration

	Disc height	Anterior osteophyte formation
Normal	Same as adjacent disc	No anterior osteophyte
Mild	75-100% of normal disc	Just detectable anterior osteophyte
Moderate	50-75% of normal disc	Clear anterior osteophyte <25% of AP diameter of corresponding vertebral body
Severe	<50% of normal disc	Clear anterior osteophyte >25% of AP diameter of corresponding vertebral body

Table S3 Prevalence of Modic changes in subgroups

	Total cervical spine		The index level	
	Baseline	1-year follow-up	Baseline	1-year follow-up
ACD	13 (17.6%)	12 (27.3%)	6 (8.1%)	10 (23.8%)
ACDF	14 (18.2%)	11 (28.9%)	8 (9.8%)	8 (26.7%)
ACDA	13 (18.1%)	5 (13.2%)	5 (6.9%)	3 (15.0%)
P value	0.995	0.190	0.731	0.624
Total	40 (17.9%)	28 (23.3%)	19 (8.6%)	21 (22.8%)

ACD: Anterior cervical discectomy
ACDF: Anterior cervical discectomy with fusion
ACDA: Anterior cervical discectomy with arthroplasty

Table S4 Modic changes on cervical segments

	None	Type I	Type II	Total
Preoperatively				
C2-C3	213	1 (0.4%)	9 (4%)	223
C3-C4	219	0	4 (1.8%)	223
C4-C5	219	0	4 (1.8%)	223
C5-C6	208	4 (1.8%)	11 (4.9)	223
C6-C7	205	5 (2.3%)	12 (5.4%)	222
C7-Th1	221	1 (0.4%)	1 (0.4%)	223
Total	1285	11 (0.8%)	41 (3.1%)	1337
Postoperatively				
C2-C3	116	1 (0.8%)	3 (2.5%)	120
C3-C4	119	0	1 (0.8%)	120
C4-C5	118	0	1 (0.8%)	119
C5-C6	91	7 (6.7%)	7 (6.7%)	105
C6-C7	91	2 (2%)	8 (7.9%)	101
C7-Th1	115	1 (9%)	1 (0.9%)	117
Total	650	11 (1.6%)	21 (3.1%)	682

Chapter 9

Does Heterotopic Ossification in Cervical Arthroplasty Affect Clinical Outcome?

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ABSTRACT

Objective

To investigate the occurrence and progression of heterotopic ossification (HO) in patients treated by anterior cervical discectomy with arthroplasty. It was also evaluated if HO affects clinical outcome and range of motion (ROM). Risk factors of HO were studied as well.

Methods

Patients who underwent anterior cervical discectomy with arthroplasty for a cervical radiculopathy due to a herniated disc from the NECK and the PROCON trial were analysed for HO at 12 and 24 months postoperatively. HO was scored according to the McAfee-Mehren classification. The index ROM was defined by a custom developed image analysis tool, and global cervical ROM was measured by Cobb's angle. Clinical outcome was evaluated by means of the Neck Disability Index and 36-Item Short Form Health Survey.

Results

The occurrence of HO was 60% at one year, and it increased to 76% at two-year follow-up. A total of 31% of patients was scored as high grade HO at one-year follow-up, and this percentage increased to 50% at two-year follow-up. Clinical outcome does not correlate to HO grade, and no risk factor for high grade HO could be identified. The ROM at the index level was significantly higher in low grade HO group than those patients with high grade HO, but in 15%-38% HO grade does not correspond to ROM.

Conclusions

HO occurs in three fourths of the patients at two years after surgery, but does not necessarily correspond to clinical outcome, nor loss or preservation of ROM. The McAfee-Mehren classification should be combined with ROM evaluation to properly study HO.

INTRODUCTION

Anterior cervical discectomy and fusion (ACDF) has been a common surgical treatment for cervical radiculopathy since it was initially described in the 1950s[1-3] and became the gold standard procedure. Nevertheless, it was shown that arthrodesis of a motion segment caused by ACDF leads to increased mechanical load at the adjacent levels[4]. Accordingly, anterior cervical discectomy with arthroplasty (ACDA) was proposed with the aim to preserve the mobility at the index level. A variety of studies have demonstrated that ACDA is able to maintain the range of motion (ROM) at the index level[5-9]. However, some adverse outcomes have been reported after cervical arthroplasty including heterotopic ossification (HO), which was first reported in 2005[10,11]. HO was postulated to lead to failure of maintenance of ROM at the target level.

HO is a phenomenon of any bone formation outside the skeletal system that occurs after surgery. It is well-known that HO occurs after arthroplasty in the lumbar spine and classified by McAfee et al.[12]. In 2006, Mehren et al.[13] published their classification system focussing on the cervical spine based on the classification presented by McAfee et al.[12]. Subsequently, several studies have been published and the incidence of HO that was reported varied considerable from 7.8% to 94.1%[14-19]. Severe HO, which was defined as grade III and IV[20], was considered to limit the ROM of the target level.

Although a recent meta-analysis reported that the severity of HO impacted clinical outcomes[20], some other studies debated it[18,21]. Thus, the prevalence of HO in patients that underwent ACDA and its impact on clinical outcome is still a controversial issue. The objective of the current study is to investigate HO in patients who were included in two randomized double-blind trials treated by ACDA for cervical radiculopathy. The correlation between HO, ROM, and clinical outcome was investigated. Risk factors of HO were studied as well.

METHODS

Study design

NECK trial

A prospective, randomized double-blind multicentre trial among patients with cervical radiculopathy due to single-level disc herniation was conducted. Patients were randomly assigned into three groups: anterior cervical discectomy with arthroplasty (ACDA; activC, Aesculap AG, Tuttlingen, Germany), anterior cervical discectomy with fusion (ACDF; Cage standalone) and anterior cervical discectomy without fusion (ACD). Patients (age 18 - 65 years old) with radicular signs and symptoms in one or both arms for at least eight weeks, in who conservative therapy failed were eligible for inclusion. All patients were diagnosed with cervical radiculopathy by a neurologist in one of the participating hospitals. If magnetic

resonance imaging (MRI) demonstrated a single-level cervical disc herniation with or without osteophyte at one level (C3-C4 to C7-Th1) in accordance with clinical signs and symptoms, patients could be included as surgical candidates for the study by the consulting neurosurgeon. Patients with previous cervical surgery, absence of motion or increased anteroposterior translation or very narrow (< 3 mm) intervertebral space or severe segmental kyphosis (> 3 degrees) at the index level on static or dynamic x-rays, neck pain only, or symptoms and signs of chronic myelopathy were excluded. A randomized design with variable block sizes was used, with allocations stratified according to centre. The protocol was approved by medical ethics committees, including an approval for randomization after anaesthetic induction. All patients gave informed consent. The design and study protocol were published previously[22].

PROCON trial

The trial design was a prospective, double-blind, single-centre randomized study, with a three-arm parallel group. Patients were randomly allocated into three groups: ACDA (Bryan disc prosthesis, Sofamor Danek, Kerkrade, the Netherlands), ACDF (Cage standalone, DePuy Spine, Johnson and Johnson, Amersfoort, the Netherlands), and ACD. Patients (age 18 - 55 years old) were eligible for inclusion with monoradicular syndrome in the arm due to single-level cervical disc degeneration disease and/ or an osteophyte at MRI. The radiological findings should be in accordance with the clinical presentation. The patients with myelopathy, previous cervical surgery, psychiatric or mental disease were excluded. The trial was approved by medical ethics committee. All patients gave informed consent. The design and study protocol were published previously[23].

Patients

Patients that were allocated to a prosthesis in the NECK trial and the PROCON trial were subject of this study.

Clinical outcomes

The Neck disability index (NDI) is a 10-item questionnaire on three different aspects: pain intensity, daily work-related activities and nonwork-related activities. Each item is scored from 0 to 5, and the total score ranges from 0 (best score) to 50 (worst score). This 50 points score was converted to a percentage (50 points=100%). The NDI is a modification of the Oswestry Low Back Pain Index and has been shown to be reliable and valid for patients with cervical pathology[24-26].

To focus on neck pain specifically, additional neck pain was evaluated using the 'neck pain intensity' section of the NDI questionnaire for all subjects from 0 (no pain) to 5 (worst imaginable pain), and disabling neck pain was defined in the research group consensus meeting as at least 3 points. Moreover, physical component summary (PCS) and mental component

summary (MCS) were derived from the 36-Item Short Form Health Survey. The PCS and MCS range from 0 to 100, with higher scores representing better self-reported health.

Demographic data were also scored for patients and included age, body mass index (BMI), sex, smoking, and alcohol use. Alcohol use was defined as no alcohol use and more than occasional drinker. These data were correlated to the severity of HO at two-year of follow-up.

Radiological evaluation

Standing lateral radiographs of the cervical spine were obtained with the patients in a neutral standing position and instructed to look straight ahead, with hips and knees extended. HO was evaluated according to the McAfee-Mehren classification system[13] (Figure 1). The patients were divided by the grade of HO[20]: low grade was defined as HO grade 0 to Grade II, and high grade was defined as grade III and IV.

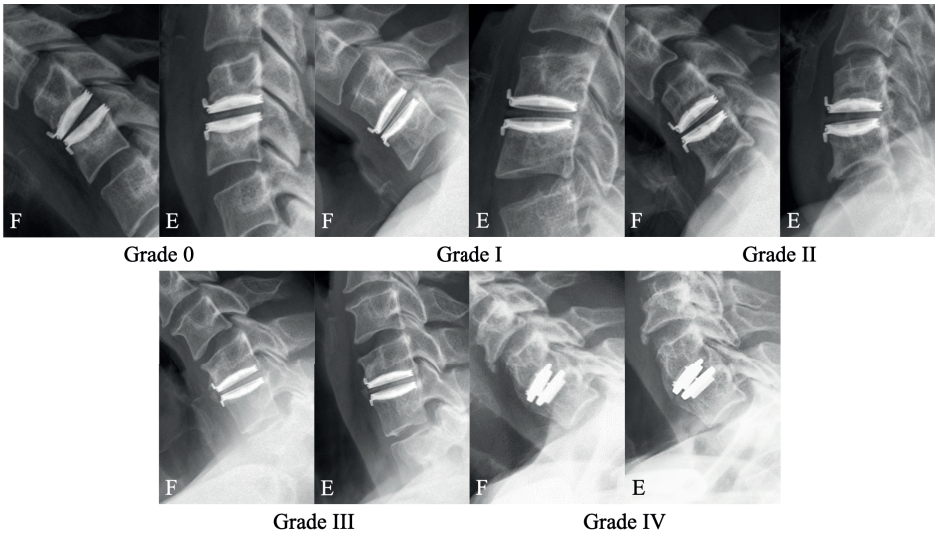

Figure 1 The grade of heterotopic ossification
Grade 0: No HO present.
Grade I: HO is detectable in the vertebral body but not in the anatomic interdiscal space.
Grade II: HO is growing into the disc space. Possible affection of the function of the prosthesis.
Grade III: Bridging ossifications which still allow movement of the prosthesis.
Grade IV: Complete fusion of the treated segment without movement in the flexion/ extension.
F: Flexion.
E: Extension.
HO: Heterotopic ossification

Additionally, flexion-extension radiographs were obtained preoperatively and at 12 and 24 months postoperatively. The ROM at the index level was defined as the intervertebral sagittal motion between full flexion and extension. The ROM at the index level was measured

with a custom developed image analysis tool (BMGO, KU Leuven, Belgium), which has a measurement error of 0.3 degree and 0.3 mm and excellent interrater and intrarater agreement (intraclass correlation coefficient >0.75)[27]. Loss of mobility was defined as ROM less than 4 degrees[28,29]. The ROM of the total cervical spine was also evaluated: the angle of C2 to C7 was measured by the lines drawn parallel to the caudal endplate of C2 and C7. The radiographs were independently evaluated by one senior neurosurgeon dedicated to spine surgery and ROM was measured by a junior medical doctor. The reviewers were not provided with any clinical information of the included patients.

Statistical analysis

All the data were presented as mean ± standard deviation. Baseline and follow-up characteristics of the ACD, ACDF and ACDA treatment group were compared using analysis of variance for continuous data and chi-square test for categorical data. Logistic regression analysis was used to determine which factors were associated with the severity of HO at two-year follow-up. The comparison on clinical parameters between low grade HO and high grade HO groups were performed by means of Student's *t*-test for continuous data. Tests were two tailed, and a P value of < 0.05 was considered significant. SPSS software, version 23.0 was used for all statistical analyses (SPSS, Inc., Chicago, IL, USA).

RESULTS

In the NECK trial, 111 patients were included and randomly assigned to ACD (38 patients), ACDF (38 patients) or ACDA (35 patients). In the PROCON trial, 142 patients were randomized into ACD (45 patients), ACDF (47 patients) or ACDA (50 patients). Therefore, 85 patients who underwent ACDA were studied. Radiographic data were available in 75 patients at one-year follow-up and 58 patients at two-year follow-up.

Demographics

Baseline characteristics are presented in Table 1. The mean age of the study population was 44.8 ± 7.7 years, ranging from 29 to 70 years.

The occurrence of heterotopic ossification

At one year after surgery, HO was absent in 30 patients (40%), scored as grade I in 13 patients (17%), grade II in nine patients (12%) and grade III in ten patients (13%). Additionally, 13 patients were evaluated to have grade IV HO (17%). Hence, 23 patients (30%) were scored as high grade HO.

At two-year follow-up, of available data of 58 patients, 14 were scored as grade 0 (24%), six patients grade I (10%), nine patients grade II (16%), 12 patients (21%) grade III and grade

IV was found in 17 patients (29%). Thus, 29 patients were scored as having high grade HO (50%).

Table 1 Demographics of the patients with low and high grade HO at two-year follow-up

	Low grade HO	High grade HO	P value
Population	29	29	
Age (years, mean ± SD)	45.8 ± 8.5	45.9 ± 7.8	0.962
Body Mass Index (mean ± SD)	27.4 ± 4.0	25.9 ± 3.2	0.160
Sex (female, No. (%))	16 (55.2%)	15 (53.6%)	0.903
Height (cm, mean ± SD)	173.4 ± 10.6	176.4 ± 10.7	0.339
Weight (kg, mean ± SD)	82.5 ± 15.8	81.4 ± 14.4	0.790
Smoking (%)	16 (55.2%)	12 (41.4%)	0.293
Alcohol use (%)	18 (62.1%)	19 (65.5%)	0.785
Operated level			
C5-C6	16	15	
C6-C7	13	14	

HO: Heterotopic ossification
SD: Standard deviation

The progression of heterotopic ossification

Fifty-five patients were available to be evaluated on progression of HO, which was compared on data between one-year and two-year follow-up. In Table 2, the evolution of HO grading is summarized. The majority of patients remained the same grade of HO at two-year follow-up in comparison to one-year follow-up. A total of 15 patients changed from low grade HO to high grade HO. (Figure 2)

Table 2 Progression of heterotopic ossification

1-year follow-up	2-year follow-up					
	0	I	II	III	IV	Total
0	13	2	2	3	4	24
I	0	4	4	2	2	12
II	0	0	2	2	2	6
III	0	0	0	4	2	6
IV	0	0	0	0	7	7
Total	13	6	8	11	17	55

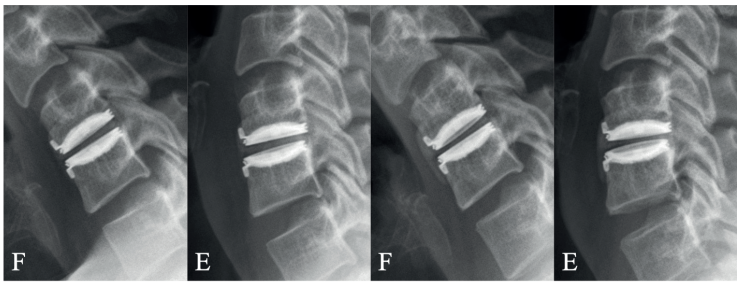

Figure 2 The pregression of heterotopic ossification over time
F: Flexion.
E: Extension.

Heterotopic ossification and clinical outcome

At two years after surgery, clinical outcomes represented by NDI, PCS and MCS, did not demonstrate a statistically significant difference between patients with low grade HO and those with high grade HO (P>0.05, Table 3). Additionally, disabling neck pain (derived from the NDI score) was present in 18% of patients with low grade HO compared with 24% of patients with high grade HO (P=0.650).

Table 3 Heterotopic ossification and clinical outcomes at 2-year follow-up

	Low grade	High grade	P
NDI	16.7 ± 20.0	17.8 ± 19.2	0.857
PCS	76.0 ± 25.6	75.9 ± 24.3	0.988
MCS	79.9 ± 21.1	74.8 ± 25.7	0.490

NDI: Neck disability index
PCS: Physical-component summary
MCS: Mental-component summary

Heterotopic ossification and range of motion

At two-year follow-up, 37% of patients (21 patients) were determined as loss of ROM (<4 degrees). The mean ROM at the index level was 10.9 ± 4.2 degrees in patients with low grade HO, which was significantly higher than ROM in patients with high grade HO (3.4 ± 3.0, P<0.001). Similarly, the patients with low grade HO were found to have a higher ROM of the total cervical spine compared with patients with high grade HO patients (57.6 ± 9.7 versus 46.5 ± 12.8, P<0.001).

Subsequently, the ROM was correlated to the HO grade on an individual level on the two-year evaluation time point. In the group of 14 patients without HO, two patients had a ROM of less than 4 degrees on the index level, and in both of those patients the total ROM was in a very low range (35 to 41 degrees). Thus, in 14% of patients with loss of ROM was observed that could not be explained by HO.

Furthermore, in the group of 29 patients with high grade HO, 11 patients had normal ROM at the target level although in two of those patients the ROM of the total cervical spine was low (36 and 38 degrees). Thus, normal ROM was observed on 38% of patients although the radiological features demonstrated high grade HO.

Finally, the progression of HO from the one-year to the two-year evaluation time point was investigated, but no particular tendency could be derived from this.

Factors associated with high grade heterotopic ossification

All the factors (age, sex, BMI, smoking, and alcohol) studied failed to demonstrate a statistical association with high grade HO at two-year follow-up (P>0.05, Table 4).

Table 4 Factors associated with high grade heterotopic ossification at 2-year follow-up

		Univariate analysis		
	Comparison	OR	95% CI	P value
Age	Per additional year of age	1.00	0.94-1.07	0.961
BMI	Per additional unit	0.89	0.75-1.05	0.160
Sex	Male (26) vs. female (31)	1.07	0.38-3.03	0.903
Smoking	Yes (28) vs. no (30)	0.57	0.20-1.62	0.295
Alcohol	Yes (37) vs. no (21)	1.16	0.40-3.39	0.785

BMI: Body mass index
OR: Odds ratio
CI: Confidence interval

DISCUSSION

The primary goal of ACDA is to preserve segmental motion close to the physiological kinematics of the cervical spine after discectomy. However, HO is a phenomenon that is regularly observed after receiving ACDA, which counteracts motion. We demonstrated that high grade HO is present in half of patients at the index level at 2 years after surgery. However, only in two thirds of these patients it led to absence of motion at the target level. Moreover, in 14% of patients who did not demonstrate HO, ROM at the target level could not be maintained.

The occurrence of HO varied in previous studies. Pimenta et al.[30] reported only one patient with grade I HO among 229 prosthesis implantations at one-year follow-up (PCM [Cervitech Rockaway, New Jersey, USA]) from an observational study on the device. Mummaneni et al.[31] described a similar result that one case of HO was detected among 276 patients in a randomized controlled multicentre trial with follow-up of two years (Prestige ST [Medtronic Sofamor Danek]). Nevertheless, several authors disputed this extremely low occurrence of HO, and reported percentages varying from 7.8% to 94.1%[14-19]. Partially, this considerable difference can be explained owing to the dynamic nature of HO, which has a progressive pattern[32]. Leung et al.[16] presented 17.8% of HO occurrence in patients at 12-month follow-up

(Bryan prosthesis), and Suchomel et al.[18] demonstrated 88% patients experienced HO at a mean follow-up period of four years (Prodisc C [Synthes, Paoli, Pennsylvania, USA]). In the study of Park et al.[19], the occurrence of HO increased from 78.8% (one year) to 94.1% (two years; Mobi-C [LDR Medical, Troyes, France]).

Our results on the activC and Bryan prostheses demonstrate results that do fit into the presented ranges of HO. However, in our study HO was correlated to ROM, which was not presented by the other authors. Remarkably, the prevalence of HO does not consequently lead to preservation or absence of motion. Therefore, judging HO only on lateral x-rays evaluating overgrowth of bone, according to the McAfee-Mehren scale, seems not to be sufficient. However, no correlation to clinical outcome could be demonstrated, in accordance with Zhou et al.[20] and Sundseth et al.[21]. Therefore, there are no practical implications of this finding. In studying maintenance of motion of the cervical spine after arthrodesis from an academic point of view, evaluation of ROM should not be omitted.

The wide variety of HO prevalence may indicate that it is associated with certain factors that are more or less represented in the population studied. Leung et al.[16] found that old age and sex (male patients) were risk factors for developing HO after ACDA. In our study, old age and sex could not be confirmed as risk factors associated with high grade HO. Neither could BMI, smoking or alcohol use be indicated as possible risk factors.

A limitation of the current study is the loss of 30% of patients at two-year follow-up, which may have an effect on this study. Another limitation may be that determining ROM on X-ray will depend on the ability and willingness of the patients to reach full flexion and extension of the cervical spine. It was evaluated whether there was an association between neck pain and limited range of motion of the whole spine, but this appeared to be absent. Improving radiological evaluation might bring a solution. Yi et al.[32] evaluated computed tomography scans after implanting prosthesis in addition to x-rays, and proposed to also evaluate computed tomography anteroposterior views to properly evaluate HO. This may be the best evaluation method to judge HO. However, to study the preservation of motion, which is the primary goal of implanting a prosthesis, evaluating dynamic x-rays is indispensable. On the other hand, because clinical outcome is not related to HO, the necessity to evaluate the occurrence of HO is questionable. This could be an argument to obtain radiographs only in case of clinically relevant complaints of the patient.

CONCLUSIONS

HO occurs in an unexpected high percentage at two years after surgery: half of patients have high grade HO. The correlation to loss of motion is not as strong as thought before, but neither could the clinical relevance of HO be demonstrated.

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Chapter 10

Comparing Heterotopic Ossification in Two Cervical Disc Prostheses

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Submitted

ABSTRACT

Objective

To compare the occurrence of heterotopic ossification (HO) between two cervical disc prostheses. Clinical outcome and range of motion (ROM) were evaluated as well.

Methods

Patients who underwent anterior cervical discectomy with arthroplasty for a cervical radiculopathy due to a herniated disc from the NECK trial (activC; metal endplates with a polyethylene inlay and a keel for primary stability) and the PROCON trial (Bryan; metal-on-polymer with titanium coated endplates without a keel) were analysed for HO at 12 and 24 months postoperatively. HO was scored according to the McAfee-Mehren classification. Segmental ROM was defined by a custom developed image analysis tool, and global cervical ROM was measured by Cobb's angle. Clinical outcome was evaluated by means of the Neck Disability Index (NDI) as well as 36-Item Short Form Health Survey (physical component summary [PCS] and mental component summary [MCS]).

Results

At two-year follow-up, the occurrence of HO was 68% in patients treated with the activC prosthesis (severe HO 55%), which was comparable with 85% (P=0.12) in patients with the Bryan disc (severe HO 44%; P=0.43). The HO progression was similar between groups. Clinically, the patients had comparable NDI, PCS and MCS at two years after surgery, and comparable improvement of clinical outcomes. The ROM of the total cervical spine in the Bryan group (56.4 ± 10.8 degrees) was significantly higher than in the activC group (49.5 ± 14.0, P=0.044) at two years after surgery.

Conclusions

The development of HO is independent on the architecture of the cervical disc prosthesis. Although ROM of the total spine was higher in the Bryan prosthesis group, this difference was not deemed clinically important, particularly because the clinical condition of patients with and without severe HO was comparable.

INTRODUCTION

Anterior cervical discectomy and fusion (ACDF) has been a common surgical treatment for cervical radiculopathy since it was initially described in the 1950s[1-3] and became the gold standard procedure. Nevertheless, it was postulated that arthrodesis of a motion segment caused by ACDF leads to increased mechanical load at the adjacent levels[4]. Accordingly, anterior cervical discectomy with arthroplasty (ACDA) was introduced with the aim to preserve the mobility at the index level. A variety of studies have demonstrated that ACDA is able to maintain the range of motion (ROM) at the index level[5-9]. However, an adverse effect has been reported after cervical arthroplasty, namely heterotopic ossification (HO), which was first reported in 2005[10,11].

HO is a phenomenon of any bone formation outside the skeletal system that occurs after surgery. It is well known that HO occurs after arthroplasty in the lumbar spine and classified by McAfee et al.[12]. In 2006, Mehren et al.[13] published their classification system focusing on the cervical spine based on the classification presented by McAfee et al.[12]. Subsequently, several studies have been published on the incidence of HO which was reported to vary considerably, from 7.8% to 94.1%[14-19]. This difference was possibly due to interobserver error[15] and the dynamic nature of HO[20]. Yi et al.[15] and Zeng et al.[21] demonstrated that different type of prosthesis could also influence the occurrence rate of HO. However, controversy exists since the difference of the occurrence of HO concerning same cervical prosthesis is still huge[16,22]. In addition, a recent meta-analysis reported that the severity of HO impacted clinical outcome[23], but some other studies debated this[18,24].

The objective of the present study is to investigate the occurrence of HO in patients who were treated by anterior cervical discectomy for cervical radiculopathy with arthroplasty using two different cervical prostheses. The clinical outcome and ROM of the cervical spine were evaluated as well.

METHODS

Study design

NECK trial

A prospective, randomized double-blind multicentre trial among patients with cervical radiculopathy due to single-level disc herniation was conducted. Patients were randomly assigned into three groups: anterior cervical discectomy with arthroplasty (ACDA; activC, Aesculap AG, Tuttlingen, Germany), anterior cervical discectomy with fusion (ACDF; Cage standalone) and anterior cervical discectomy without fusion (ACD). The protocol was approved by medical ethics committees, including an approval for randomization after

anaesthetic induction. All patients gave informed consent. The design and study protocol were published previously[25].

PROCON trial

The trial design was a prospective, double-blind, single centre randomized study, with a three-arm parallel group. Patients were randomly allocated into three groups: ACDA (Bryan disc prosthesis, Sofamor Danek, Kerkrade, the Netherlands), ACDF (Cage standalone, DePuy Spine, Johnson and Johnson, Amersfoort, the Netherlands), and ACD. The trial was approved by medical ethics committee. All patients gave informed consent. The design and study protocol were published previously[26].

Patients and disc prostheses

Patients that were allocated to a prosthesis in the NECK trial and PROCON trial were subject of this study.

The activC device is composed of two flat Cobalt-Chrome-Molybden alloy metal endplate components with spikes on the superior endplate and an inferior endplate and a keel for primary stability. The inferior prosthesis plate has an integrated polyethylene inlay[27].

The Bryan disc is a one-piece, biarticulating, metal-on-polymer, unconstrained device with a fully variable instantaneous axis of rotation[28]. Initial stability is achieved by precision milling of the vertebral endplates, and long-term stability is provided by bone growth into the porous-coated titanium alloy endplates[29].

Clinical outcomes

Neck disability index (NDI) is a 10-item questionnaire on three different aspects: pain intensity, daily work-related activities and nonwork-related activities. Each item is scored from 0 to 5 and the total score ranges from 0 (best score) to 50 (worst score). This 50 points score was converted to a percentage (50 points=100%). The NDI is a modification of the Oswestry Low Back Pain Index and has been shown to be reliable and valid for patients with cervical pathology[30-32].

Moreover, physical component summary (PCS) and mental component summary (MCS) were derived from the 36-Item Short Form Health Survey. The PCS and MCS range from 0 to 100, with higher scores representing better self-reported health.

Radiological evaluation

Lateral radiographs of the cervical spine were obtained with the patients in a neutral standing position and instructed to look straight ahead, with hips and knees extended. HO was evaluated according to the McAfee-Mehren classification system[13] (Table 1). The patients were divided by the grade of HO[23]: mild HO was defined as grade 0 to Grade II, and severe HO was defined as grade III and IV.

Table 1 The classification of heterotopic ossification

Grade	Classification
Grade 0	No HO present
Grade I	HO is detectable in front of the vertebral body but not in the anatomic interdiscal space
Grade II	HO is growing into the disc space. Possible affection of the function of the prosthesis
Grade III	Bridging ossifications which still allow movement of the prosthesis
Grade IV	Complete fusion of the treated segment without movement in the flexion/ extension

HO: Heterotopic ossification

Flexion-extension radiographs were obtained preoperatively and at 12 and 24 months postoperatively. The ROM at the index level was defined as the intervertebral sagittal motion between full flexion and extension. The ROM at index level was measured with a custom developed image analysis tool (BMGO, KU Leuven, Belgium), which has a measurement error of 0.3 degree and 0.3 mm and excellent interrater and intrarater agreement (intraclass correlation coefficient >0.75)[33]. The ROM of the total cervical spine was evaluated using Cobb's method: the angle of C2 to C7 was measured between the lines drawn parallel to the caudal endplates of C2 and C7[34].

HO was independently evaluated by one senior neurosurgeon (CVL) dedicated to spine surgery and ROM was measured by a junior medical doctor (XY). The reviewers were not provided with any clinical information of the included patients.

Statistical analysis

All the data were presented as mean ± standard deviation. Data of the activC group and Bryan group were compared using Student's *t*-test for continuous data and chi-square test for categorical data. Paired *t*-test was performed on the comparison of segmental ROM between baseline and two-year follow-up. Tests were two tailed, and a P value of < 0.05 was considered significant. SPSS software, version 25.0 was used for all statistical analyses (SPSS, Inc., Chicago, IL, USA).

RESULTS

Demographics

In the NECK trial, 35 patients were randomly assigned to the activC group, and 48 patients were assigned to the Bryan group in the PROCON trial. There was no difference between the two groups in baseline characteristics (Table 2).

Table 2 Demographics of the patients

	ActivC group	Bryan group	P value
Population	35	48	
Age (years, mean ± SD)	46.5 ± 8.7	43.6 ± 6.7	0.086
Body Mass Index (mean ± SD)	26.9 ± 3.7	26.6 ± 4.4	0.725
Sex (female, No. (%))	18 (52.9%)	25 (52.4%)	0.939
Height (cm, mean ± SD)	174.3 ± 11.2	175.3 ± 9.1	0.663
Weight (kg, mean ± SD)	82.1 ± 14.3	82.2 ± 17.2	0.978
Smoking (%)	14 (40.0%)	25 (52.1%)	0.276
Operated level			
C5-C6	19	22	
C6-C7	16	26	

SD: Standard deviation

The occurrence of heterotopic ossification

At two-year follow-up in the activC group, HO was absent in ten patients (32%) and was present as grade I in one patient (3%), grade II in three patients (10%) and grade III in four patients (13%). 13 patients were evaluated to have grade IV (42%). In the Bryan patient group at two-year follow-up, four patients had no HO (15%), five patients had grade I HO (19%), six patients had grade II (22%), eight patients had grade III (30%) and grade IV was found in four patients (15%) (Figure 1). Consequently, the overall HO occurrence of the activC group was 68%, which is comparable with 85% HO in the Bryan group (P=0.121). Furthermore, severe HO was present in 55% of the patients that received an activC prosthesis and in 44% of the patients that received a Bryan disc (P=0.430).

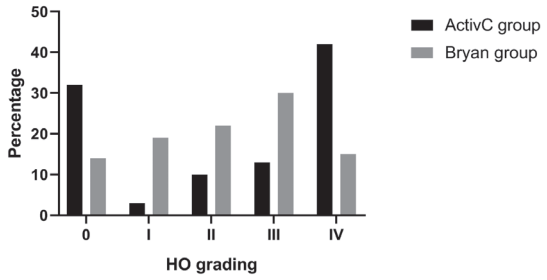

Figure 1 The occurrence of heterotopic ossification at two-year follow-up

The progression of heterotopic ossification

In Table 3, the progression of HO grading is summarized. In the activC group, 48% of the 29 patients that demonstrated mild HO at one-year follow-up to severe HO at two-year follow-up. This increase was comparable to 42% of the 26 patients in the Bryan group that increased from mild to severe HO (P=0.657).

Table 3 Progression of heterotopic ossification

ActivC group						
1-year follow-up	2-year follow-up					
	0	I	II	III	IV	Total
0	9	0	2	3	4	18
I	0	1	0	0	2	3
II	0	0	0	0	2	2
III	0	0	0	1	1	2
IV	0	0	0	0	4	4
Total	9	1	2	4	13	29
Bryan group						
1-year follow-up	2-year follow-up					
	0	I	II	III	IV	Total
0	4	2	0	0	0	6
I	0	3	4	2	0	9
II	0	0	2	2	0	4
III	0	0	0	3	1	4
IV	0	0	0	0	3	3
Total	4	5	6	7	4	26

Comparison on clinical outcome

At two years after surgery, the mean NDI value decreased 25.7 points from baseline in the activC group, which is comparable with a decrease of 28.0 points in the Bryan group (P=0.879). The PCS mean value improved 31.3 points in the activC group, compared to an improvement of 33.8 points in the Bryan group (P=0.987). Likewise, the patients in both groups had an increased MCS value without a statistically significant difference (16.8 versus 19.9, P=0.702) (Table 4). No correlation between clinical outcome and severe HO could be demonstrated, neither in the activC group, the Bryan group, nor in the combination group (Table 5).

Table 4 The improvement of clinical outcome between activC and Bryan

	ActivC group			Bryan group			P value
	Baseline	2-year FU	Difference	Baseline	2-year FU	Difference	
NDI	45.8 ± 17.1	20.1 ± 22.0	25.7	40.4 ± 15.0	12.4 ±15.8	28.0	0.879
PCS	41.0 ± 14.7	72.2 ± 27.3	31.3	42.6 ± 15.6	76.4 ± 24.8	33.8	0.984
MCS	57.0 ± 24.5	73.8 ± 25.7	16.8	59.0 ± 22.8	78.9 ± 18.7	19.9	0.702

FU: Follow up
NDI: Neck Disability Index
PCS: Physical-component summary
MCS: Mental-component summary

Table 5 Clinical outcome and the severity of HO

		Mild HO	Severe HO	P value
ActivC group	NDI	19.5 ± 21.7	18.8 ± 20.7	0.933
	PCS	73.1 ± 27.2	74.2 ± 25.8	0.915
	MCS	75.3 ± 24.0	75.8 ± 27.4	0.961
Bryan group	NDI	13.4 ± 18.4	15.3 ± 15.3	0.832
	PCS	79.6 ± 24.6	80.4 ± 21.1	0.947
	MCS	85.5 ± 16.5	72.2 ± 22.3	0.206
Combination group	NDI	16.7 ± 20.0	17.8 ± 19.2	0.857
	PCS	76.0 ± 25.6	75.9 ± 24.3	0.988
	MCS	79.9 ± 21.1	74.8 ± 25.7	0.490

HO: Heterotopic ossification
NDI: Neck Disability Index
PCS: Physical-component summary
MCS: Mental-component summary

Comparison on range of motion

At baseline, there was no difference in segmental ROM between the activC group (8.3 ± 4.4 degrees) and the Bryan group (7.7 ± 3.7 degrees, P=0.609). Likewise, no difference was detected in ROM of the total cervical spine (44.9 ± 17.3 versus 51.4 ± 16.0 degrees, P=0.215). At two-year follow-up, the segmental ROM in both groups was comparable to baseline: 5.7 ± 5.5 degrees in the activC group (P=0.071), and 8.2 ± 4.7 degrees in Bryan group (P=0.277); no significant difference between the activC and Bryan group was present (P=0.065). At two-year follow-up, the ROM of the total cervical spine differed between the groups: in the Bryan group the ROM of the total cervical spine (56.4 ± 10.8 degrees) was significantly larger than in the activC group (49.5 ± 14.0, P=0.044).

DISCUSSION

The initial purpose of ACDA is to preserve segmental motion close to the physiological kinematics of the cervical spine after discectomy. However, HO is a phenomenon that is observed with varying reported incidences after implanting a cervical prosthesis. In the current article it was demonstrated that the HO was present in the vast majority of patients two years after surgery and that the occurrence of severe HO was present in almost half of the patients. The phenomenon was independent of the type of implant used. However, the occurrence of HO had no detrimental influence on clinical outcome.

A difference in architecture between the Bryan and the activC prosthesis is the presence of a keel in the activC prosthesis. The purpose of a keel is to affirm the prosthesis tot the end plate in a solid way. However, a keel violates the cortical surface of the end plate and this can

hypothetically result in overgrowth of bone, and thus in HO[15]. In the present study, however, the presence or absence of a keel did apparently not influence the formation and progression of HO.

Although the ROM of the total cervical spine was larger in the Bryan prosthesis group, this did not affect clinical outcome. A larger ROM in the Bryan prosthesis group may (partially) be explained by the lower proportion of patients with severe HO in the Bryan group. The absence of a correlation between a ROM and clinical condition corresponds with our previous result demonstrating that there is no correlation between ROM and clinical outcome after cervical discectomy[35].

A limitation of the current study may be that determining ROM on X-ray is dependent on the ability and willingness of the patients to reach full flexion and extension of the cervical spine. The inability to demonstrate full flexion/extension may be due to neck pain. It was evaluated whether there was an association between neck pain and limited range of motion of the cervical spine, but this appeared to be absent. Another limitation may be that HO is sub-optimally evaluated on X-ray. Yi et al.[20] evaluated computed tomography scans after implanting prosthesis in addition to x-ray and found that severe HO allowed segmental motion, while mild HO could have no motion in some case. They proposed to also evaluate computed tomography anteroposterior views to properly evaluate HO. This may be the best evaluation method to judge HO. However, in order to study the preservation of motion, which is the primary goal of implanting a prosthesis, evaluating dynamic X-ray is indispensable. On the other hand, since clinical outcome is not related to HO, the necessity to evaluate the occurrence of HO is questionable. This could be an argument to obtain radiographs only in case of clinically relevant complaints of the patient.

CONCLUSIONS

The development of HO is present in the vast majority of patients receiving a prosthesis but independent on the architecture of the cervical disc prosthesis. The presence of HO did not influence clinical outcome.

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Chapter 11

Discussion & Conclusions

The incidence of adjacent segment degeneration in motion preservation surgery

According to the evidence presented in chapter 2, literature review delivers the first remarkable finding of this thesis. Although the cervical disc prosthesis was introduced in anterior spine surgery to prevent adjacent segment degeneration (ASD), our literature review demonstrated that the occurrence of ASD was only studied marginally. In none of the publications concerning prosthesis evaluation in patients suffering exclusively from cervical radiculopathy, radiological evaluation on ASD was studied. In studies concerning prosthesis evaluation in mixed patient populations, radiological evaluation of ASD was performed only in a limited number of articles. And even if it was mentioned, the method to study ASD was repeatedly insufficient: intervertebral disc degeneration is deemed to be a physiological process[1-5], and therefore some extent of degeneration at the adjacent disc levels is expected to be already present at baseline. In order to radiologically identify pre-existing degeneration, it is essential to compare postoperative signs of degeneration (disc height and osteophyte formation) to baseline degeneration. Only six[6-11] of 38 mixed population studies adequately studied radiological ASD by comparing to baseline data. In these articles, at baseline, ASD was already present in a high percentage (50%)[6] of cases. This is to be expected since it concerns a population suffering from myelopathy which is degenerative by diagnosis. Literature demonstrates a tendency to more ASD in the fusion groups, but no statistically significant differences could be demonstrated.

Our study is thus the first to evaluate ASD in a cohort consisting only of radiculopathy patients. Evaluating ASD in the NECK and PROCON trial was done by studying the decrease of disc height and the severity of osteophyte formation on X-rays at baseline and postoperatively[4] at both the superior and the inferior level. We demonstrated that baseline ASD was present in 34% of patients, which was lower in comparison to the data that we found in our review. This is well attributable to the study population: the 50% baseline ASD was demonstrated in the mixed study population, as mentioned in the previous paragraph. ASD increased to 58% at two-year follow-up and we could not demonstrate a difference in the incidence and progression of ASD in patients who underwent cervical arthrodesis (ACD or ACDF) and patients who received a cervical prosthesis (Chapter 3). Therefore, the proclaimed advantage of implanting a prosthesis to prevent ASD could not be established.

However, one could argue that our power calculations were not aiming at finding a difference between the groups based on ASD since they were based on a finding a difference in NDI. Originally though, the power calculation was indeed based on a difference in symptomatically relevant ASD between the groups according to data provided by Robertson et al.[10]. In the original NECK trial protocol, the following was mentioned: 'the sample size was calculated according to the incidence of clinical ASD of 2% after ACDA and 7% after ACDF reported by Robertson et al.[10]. To this end, a total of 750 patients are needed in this study.' However, after a few years, it became obvious that it would need more than 15 years to accomplish the trial. Therefore, in the NECK trial, we subsequently changed the protocol

and made new calculations using the neck disability index (NDI) as the primary outcome parameter to justify the clinically relevant benefit after ACDA. On the other hand, after a double check on the original full text, the incidence of symptomatic ASD in the ACDF group described by Robertson et al. is 0 rather than 2%. In their study, symptomatic ASD was defined widely, which is patients who manifested as neck, shoulder, and/or arm pain that required medical attention during the 24-month period, degenerative disc disease at the adjacent level, and the appearance of a ruptured cervical disc at the adjacent level. Moreover, they also reported that the incidence of radiological ASD was 35% in ACDF and 18% in ACDA, which was described as new anterior osteophyte formation or enlargement of existing osteophyte, increased or new narrowing of a disc space, and new or increased calcification. However, the correlation between symptomatic ASD and radiological ASD is not clear in this study. Since it is still debatable on the definition of symptomatic ASD as both the rate of reoperation at the adjacent levels and the development of new clinical symptoms corresponding to the adjacent levels can be used as the measurement, it would be interesting to evaluate the incidence of radiological ASD in the NECK trial as well.

Adjacent segment degeneration and range of motion

Hypothetically, it is thought that maintaining range of motion (ROM) at the target level will result in prevention from ASD and subsequently in better functional outcome in the long term. We thus studied whether ROM was maintained at the target level. In the majority of patients, ROM was indeed preserved after implanting a cervical prosthesis, and not preserved after ACD or ACDF. However, maintaining motion did not correlate to the incidence or positive progression of ASD at two years after surgery. We also studied the correlation between ROM of the whole cervical spine and ASD and could not demonstrate a correlation either.

We did notice however that ROM at the index level was not consequently absent in the ACD and ACDF group and was not consequently maintained in the ACDA group. In the present study, it was demonstrated that 63% of patients with ACDA had radiologically preserved ROM (>4 degrees) versus 37% that did not at two-year follow-up. We therefore additionally evaluated the correlation between ASD and ROM on the basis of preservation of ROM. Again, no correlation could be established between preserved ROM and the absence of ASD. Furthermore, this correlation was studied in all patients irrespective of the surgical method. We demonstrated that the percentage of patients with the presence of ASD and patients with positive progression of ASD was not significantly higher in patients with loss of ROM than in those with motion preservation at two-year follow-up.

It is generally presumed that the development of ASD is a slow process, and that therefore long-term follow-up periods are essential in order to properly judge the occurrence of ASD. However, an increase of approximately 20% of ASD (or 20% of patients with positive progression of ASD) within the first two years after surgery, justifies the conclusion that ASD is not significantly dependent on the preservation of motion at the index level.

Therefore, no advantage of a cervical disc prosthesis was demonstrated. Considering the higher costs and the longer operating time, it is not recommended to implant a prothesis in patients with singe-level cervical radiculopathy.

Does cervical sagittal alignment correlate with adjacent segment degeneration?

The cervical spine has a crucial role in compensating a distorted global spinal balance. In order to maintain horizontal gaze, the cervical spine will compensate[12]. Regularly, global sagittal imbalance, if present at all, will only be present in a very mild form in the average patient with cervical radiculopathy. Surgical interventions can however possibly interfere with cervical sagittal alignment. Subsequently, even minor cervical spine balance compensation mechanisms may cause accelerated degeneration of the cervical spine segments. Therefore, an acquired sagittal imbalance by anterior discectomy may influence ASD.

In Chapter 5, cervical sagittal alignment was demonstrated not to be altered by anterior discectomy at two-year follow-up. The alleged superiority of maintaining cervical sagittal alignment in arthroplasty was not confirmed. The occipito-cervical angle measured by occipital cervical inclination (OCI), being crucial in maintaining horizontal gaze, was identified as an important factor associated with radiological ASD.

OCI is a relatively new radiological parameter of the angle between the occiput and the cervical spine proposed by Yoon et al.[13] in 2017. Theoretically, the occipito-cervical angle is dictated by horizontal gaze, and if this angle is imbalanced it may well lead to compensation of subaxial cervical curvature, which will eventually lead to accelerated degeneration of the cervical spine[14,15]. This could explain the strong correlation of OCI with ASD detected in the current study. Notably, although there was significantly more ASD in patients with a higher OCI, the postoperative OCI angle did not change. Therefore, the result of this study suggests that accelerated degeneration of the cervical spine is dictated by the OCI angle. Thus, ASD of the cervical spine can be predicted if the OCI is known. Ideally a cut-off point of the OCI would be available. ASD is determined in this study in three ways and therefore three different values are available: for non ASD an angle of 102 to 104 degrees was measured, and for ASD angles varying between 108 and 113 degrees were observed. Yoon et al.[13] evaluated 200 normal, sagittally balanced patients (for both the whole spine and cervical spine) who were with no instability, spondylosis, degenerative change, deformity, or fracture. It was demonstrated that OCI was 103 degrees for male patients and 102 degrees for female patients, which is in agreement with the OCI value of non ASD patients reported in the current study. This suggests that an OCI angle of 102 to 104 degrees may indicate a sagittally balanced cervical spine, while the angle with higher degrees would have a risk to occur cervical disc degeneration, especially for those patients with more than 108 degrees. However, this 'normal' OCI value needs to be validated in healthy people with a large population. The cut-off value for OCI needs to be more accurate as well since the current study only shows a six to nine degrees difference between patients with and without ASD, which is not practical in the daily practice.

In the current study, no correlation between clinical outcome and cervical sagittal balance parameters could be demonstrated. The C2-C7 sagittal vertical axis (SVA) and T1 slope did not change in follow-up of surgery, the C2-C7 lordosis only increased minimally, and they did not demonstrate a correlation with ASD. Therefore, an absence of correlation to the clinical outcome is not surprising. However, previous studies did demonstrate an association between sagittal alignment parameters to the quality of life[12,16-18]. Tang et al.[19] found that the C2-C7 SVA was negatively correlated with physical-component summary (PCS) derived from the SF-36 and positively correlated with NDI scores after multilevel cervical posterior fusion. Hyun et al.[20] found that C2-C7 SVA greater than 43.5 mm was corresponded to severe NDI (>25). Nevertheless, Jeon et al.[21] and Kwon et al.[22], which compared similar radiographic parameters with NDI and visual analogue scale (VAS), reported that no cervical sagittal alignment parameters were significantly correlated with clinical outcome after ACDF surgery with three levels and two levels, respectively, which are consistent with our results. It has to be noted though that these authors described different surgical approaches. Tang et al.[19] and Hyun et al.[20] reported on patients with posterior cervical fusion surgery. Jeon et al.[21] and Kwon et al.[22] reported on multilevel anterior fusion surgery of the cervical spine and demonstrated threshold values for C2-C7 SVA of 40 mm[19] and 43.5 mm[20] in contrast to the values that we reported in the majority of patients (mean value: 20.6-22.5 mm).

Do Modic changes correlate with cervical disc degeneration or clinical condition?

Literature is scarce on Modic changes (MCs) in the cervical spine. However, from the literature available a positive association of cervical MCs with the prevalence of neck pain or disability and with the prevalence of disc degeneration was demonstrated. It has to be noted though that there are large variations in patient populations in which MCs are studied and that this explains the huge variation of the presence of MCs that is reported in literature (5% to 40%). All of the included studies demonstrate that MCs type II are predominant in the cervical spine and that C5-6 is the most frequent level followed by C6-7 at which MCs are diagnosed. As the endplates of C5-C7 sustain more weight than the higher levels and vertebrae are less limited in their excursion, greater momentum on the vertebral endplates are transmitted.

With a high quality of evidence, disc degeneration was positively correlated with MCs in the cervical spine, suggesting that the patients with MCs have more severe cervical disc degeneration. The only result of non-correlation was described by Davies et al.[23], who studied a small number of discs (106 discs) in comparison to the other studies (studying 256 to 6138 discs). Nevertheless, this is the only study using a histological method to evaluate disc degeneration. Since histological evaluation of intervertebral disc tissue is deemed the most accurate and sensitive method of identifying disc degeneration[24,25], more studies are needed to clarify the correlation between cervical disc degeneration assessed by histological methods and MCs.

Our own results demonstrated that one fifth of patients were detected to have MCs, being predominantly type II. One year after cervical discectomy, the prevalence of MCs increased to 30%, and remained predominantly type II. If observing MCs at the target level, 9% of patients had preoperative MCs, and this increased to 23% at one-year follow-up.

Although literature revealed an association between the presence of MCs with neck pain in the cervical spine, our data did not support this finding. This may be due to the absence of a proper scoring system for neck pain in these papers. In the present study, using accurate and representative measures for neck pain, it was shown both at baseline and at one year after surgery, that patients with and without MCs reported disabling neck pain in a comparable proportion. Our finding that there is absence of a correlation between MCs and neck pain is in agreement with earlier findings in our group by El Barzouhi et al.[26], which did not demonstrate a correlation between back pain and MCs. In follow-up research by Djuric et al.[27] though, an MCs dependent correlation between back pain/leg pain and the presence of macrophages in disc tissue in patients operated for sciatica due to a herniated disc was demonstrated. It is very interesting to evaluate whether that correlation is also valid for the cervical spine. Future research in our group is focussing on that.

Additionally, we studied the correlation between MCs and radiculopathy. MCs were hypothesized to represent an inflammatory process involving low virulent anaerobic bacteria[28], which may influence the spinal root and thus influence pain in the arm. The correlation of MCs with disabling arm pain was however not confirmed in the present study. This is consistent with a previous report from Kressig et al.[29], which studied 44 patients with cervical radiculopathy and which reported arm pain with the numerical rating scale.

Does the size of cervical disc herniation affect clinical condition?

Cervical radiculopathy is diagnosed based on anamnestic details and physical examination. Imaging of the cervical spine can reveal whether the radiculopathy is caused by compression of the spinal root, for instance by a herniated disc. Size and contour of disc herniations can be measured and identified on magnetic resonance image (MRI), as can the size and proportions of the spinal canal[30], Our data could not find a correlation between the size of disc herniation measured on MRI and the clinical condition at baseline. Neither did the size of the disc herniation correlate to outcome and this is thus not predictive for clinical outcome after surgical treatment at two-year follow-up.

Regarding the patients with cervical radiculopathy, roughly 80-88% of them will improve within four weeks of nonoperative management[31,32]. If severe symptoms persist, spinal surgery as a treatment modality is considered, and it would be of significance if the size of the herniation would correlate to the clinical burden. This cannot be confirmed in the current study. Thus, not only is the presence of a disc herniation on MRI not distinctive for the presence of clinical signs, neither is the size of the hernia indicative for the severity of complaints.

Similarly, the correlation between the size of disc herniation and clinical symptoms was also absent in lumbar spine: el Barzouhi et al. demonstrated that the predictive value of the size of disc herniation at baseline in decision making for lumbar disc surgery is absent[33], and that the size of disc herniation at baseline measured on MRI did not correlate to outcome at one-year follow-up[34]. Eventually, the MRI performed at one-year follow-up in patients with surgical treatment did not distinguish between those with a favourable outcome and those with an unfavourable outcome[35].

These data indicate that the value of MRI for patients with cervical radiculopathy that do not require surgery at that point is minimal. An MRI can only be helpful if the treating physician wants to exclude another compressing cause for the radiculopathy like a tumour for instance. However, literature does not provide evidence that tumours are demonstrated on MRI if other alarm symptoms (loss of body weight, tiredness etc.) are absent. It may be that the patients need reassurance and that an MRI can be helpful in that process. Furthermore, it is debatable whether society should bear those costs. It would be interesting to find out how much the patient would be willing to pay for this reassurance by an MRI.

Does heterotopic ossification in cervical arthroplasty affect clinical outcome?

As one of the major complications after receiving ACDA, which may counteract the ROM of the cervical spine, the incidence of heterotopic ossification **(**HO) was reported with huge variation, from 17.8% to 94.1%[36]. The published results of HO from randomized controlled trails (RCT) are scarce and of very low evidence[37].

It was demonstrated in chapter 9 that high grade HO is present in half of patients at the index level at two years after surgery. However, only in two thirds of these patients that led to the absence of motion at the target level. Moreover, ROM at the index level could not be maintained in 14% of patients that did not demonstrate HO.

The occurrence of HO varied in previous studies. Pimenta et al.[38] reported only one patient with grade I HO among 229 prosthesis implantations at one-year follow-up (PCM prosthesis). However, these are results from an observational study on the device, being industry sponsored. Mummaneni et al.[39] described a similar result that one case of HO was detected among 276 patients in a multicentre RCT with follow-up of two years (Prestige prosthesis). Although this was a comparative study, it was also industry sponsored. Nevertheless, several authors disputed this extremely low occurrence of HO, and reported percentages varying from 7.8% to 94.1%[40-45]. Partially, this considerable difference can be explained due to the dynamic nature of HO, which has a progressive pattern[46]. Leung et al.[42] presented 17.8% of HO occurrence in patients at 12-month follow-up (Bryan prosthesis), and Suchomel et al.[44] demonstrated 88% patients experienced HO at a mean follow-up period of four years (Prodisc-C prosthesis). In the study of Park et al.[45], the occurrence of HO increased from 78.8% (one year) to 94.1% (two years; Mobi-C prosthesis).

The findings on the activC and Bryan prostheses demonstrate results that do fit into the presented ranges of HO. However, in the present study, HO was correlated to ROM, which was not presented by the other authors. Remarkably, the prevalence of HO does not consequently lead to preservation or absence of motion. Therefore, judging HO only on lateral x-rays evaluating overgrowth of bone, according to the McAfee-Mehren scale, seems not to be sufficient. However, no correlation to clinical outcome could be demonstrated, in accordance with Zhou et al.[47] and Sundseth et al.[48]. Therefore, there are no practical implications of this finding. In studying maintenance of motion of the cervical spine after arthrodesis from an academic point of view though, evaluation of ROM should not be omitted.

Since the difference of architecture of the cervical disc prosthesis may affect development HO, in the Chapter 10, the incidence of HO were compared between activC and Bryan prostheses. It was demonstrated that the phenomenon of HO was independent of the type of implant used. However, the occurrence of HO had no detrimental influence on clinical outcome.

A difference in architecture between the activC and the Bryan prosthesis is the presence of a keel in the activC prosthesis. The purpose of a keel is to affirm the prosthesis tot the end plate in a solid way. However, a keel violates the cortical surface of the end plate and this can hypothetically result in overgrowth of bone, and thus in HO[41]. In the present study, the presence or absence of a keel did apparently not influence the formation and progression of HO. Although the ROM of the total cervical spine was larger in the Bryan prosthesis group, this did not affect clinical outcome. A larger ROM in the Bryan prosthesis group may (partially) be explained by the lower proportion of patients with severe HO in the Bryan group. The absence of a correlation between a ROM and clinical condition corresponds with our previous result demonstrating that there is no correlation between ROM and clinical outcome after cervical discectomy[49].

In conclusion, HO occurs in an unexpected high percentage at two years after surgery. The correlation to loss of motion is not as strong as thought before, but neither could the clinical relevance of HO be demonstrated.

Current status and future perspective

The role of cervical prosthesis in patients with single-level radiculopathy should be rethought. The results of this thesis counteract the intuitive feeling of the advantages of implanting a prosthesis after anterior cervical discectomy. A limitation is the relatively short follow-up of two years. We are currently evaluating the five-year follow-up data, and this may lead to even more convincing data. The absence of a correlation between motion preservation and the presence of ASD from the two-year data are however so strong, that we would be surprised if other conclusions would be revealed.

Another limitation is the analysis of ASD in which we focused on radiological ASD. Clinically relevant ASD would be represented by invalidating radicular symptoms due to

degeneration at the adjacent level(s). If these complaints would be significantly invalidating, subsequent surgery would follow. The number of reoperations in the three groups for this diagnosis, would therefore be a suitable measure for clinical ASD. However, the number of reoperations in the NECK trial are too small to draw meaningful conclusions. Therefore, in evaluating the five-year follow-up data, the reoperation data will be combined with the long-term follow-up data of the PROCON trial, focusing on reoperations. We aim to further elucidate the correlation between clinically relevant ASD and preserved ROM.

The presence of MCs was correlated to radiological degeneration at the global cervical spine at baseline. However, this correlation could not be confirmed in the analysis considering only the target level and disappeared at one year after surgery. The absence of such correlation at one-year follow-up may be due to the lower number of MRIs that were available. Furthermore, it would have led to stronger results if the VAS neck pain was assessed for the patients in the PROCON study too. Finally, the prosthesis lacks proper evaluation of MCs at the adjacent levels, which lowered the number of patients in which MCs could be studied even more. Future studies are needed to investigate the change of the prevalence of MCs between the pre- and post-operative condition.

MCs are believed to represent the inflammatory and degenerative condition of the endplates. In our research group, it was found that an MCs dependent correlation between back pain/leg pain and the presence of macrophages in disc tissue in patients operated for sciatica due to a herniated disc is present. Future research will be focussing on whether that correlation is also valid for the cervical spine.

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Chapter 12

Summary

Cervical motion preservation prostheses are considered a developing technology, with widespread clinical use beginning in the early 2000s. They are developed to reduce adjacent segment degeneration (ASD) in the postsurgical follow-up by maintaining range of motion (ROM). However, it is still a controversial issue. The main objective of this thesis was to uncover the relationship between preserved motion and radiological ASD in patients with single-level cervical radiculopathy. Other factors which may be correlated to ASD were studied as well.

The basis of this study was the NECK and PROCON trial: two prospective randomized controlled trials among patients with single-level cervical radiculopathy. Anterior cervical discectomy with prosthesis (ACDA) was compared to a conventional approach with (ACDF) or without an interbody cage (ACD). No significant differences in clinical outcomes after two-year follow-up were demonstrated. The current thesis considers the radiological outcome data.

Chapter 1 gives an introduction and an history of surgical treatment of cervical radiculopathy. At present, ACDF is defined as the gold standard for cervical disc herniation surgery since clinical researchers have demonstrated excellent clinical outcome with low complication rates in long term follow-up. Subsequently, the concept of ASD was proposed since arthrodesis of a motion segment was documented to lead to increased mechanical load and stress at the levels adjacent to the fusion site. Cervical prosthesis was developed to prevent ASD and thereby avoid neck pain and disability in postoperative follow-up by motion preservation. However, the benefits of implanting a cervical prosthesis remain controversial and the basis of preventing ASD by maintaining ROM has not been confirmed.

Chapter 2 describes the results of a systematic review on radiological follow-up after implanting cervical disc prosthesis in anterior discectomy. Radiological signs of ASD were present at baseline in 50% of patients, and there is a low-level evidence that this increased more (10%–20%) in the fusion group at long-term follow-up. However, this was only studied in the mixed study population, which is degenerative by diagnosis.

Chapter 3 reports on the correlation between the size of the disc herniation and the clinical condition, as well as the prognostic value of MRI findings in relation to clinical outcome in patients with cervical radiculopathy. At baseline, the patients in the mild herniation group had a comparable neck disability index (NDI) and 36-Item Short Form Health Survey (SF-36) to the patients in the severe herniation group. Likewise, both disabling arm pain and disabling neck pain were comparable in the mild and severe herniation group. At two years after surgery, no difference was found in any of the clinical parameters between the two groups. Therefore, in patients suffering from cervical radiculopathy, the size of disc herniation does not correlate to the severity of clinical symptoms at baseline and does not allow to predict clinical outcome after surgical treatment at two-year follow-up.

Chapter 4 reports on the incidence of radiological ASD comparing cervical prosthesis surgery to cervical arthrodesis surgery. ASD was present in 34% of patients at baseline and in-

creased to 59% at two-year follow-up in the arthrodesis groups (ACD and ACDF combined), and to 56% in the arthroplasty group. Progression of ASD was present in 29% of patients in the arthrodesis group and in 31% of patients in the arthroplasty group at two-year follow-up. It was demonstrated that radiological ASD occurs in similarly in patients that were subjected to arthrodesis in cervical radiculopathy and in patients that received arthroplasty to maintain motion.

Chapter 5 reports on the relationship between ROM of the cervical spine (both at the target level and of the global cervical spine) and the presence of radiological ASD after cervical discectomy. In the prosthesis group, 63% patients with a preserved ROM (> 4 degrees at the target level) did not show a significantly lower incidence of ASD or less positive ASD progression than patients with an immobile cervical segment. In the analysis irrespective of surgical methods, no correlation was demonstrated between ROM and ASD, and neither for neck disability. Therefore, the advantage of a cervical motion preserving device to reduce accelerated degeneration at the adjacent levels is not confirmed in the present chapter.

Chapter 6 reports on the relationship between sagittal alignment and the presence of radiological ASD in the cervical spine. It was demonstrated that the cervical sagittal alignment parameters were comparable between the three treatment groups, both at baseline and at two-year follow-up. Irrespective of the surgical method used, C2-C7 lordosis was found to increase from 11 to 13 degrees, but the other parameters remained stable during follow-up. Only the occipito-cervical inclination (OCI) with higher degrees (108 to 113 degrees) was demonstrated to be associated with the presence and positive progression of radiological ASD, both at baseline and at two-year follow-up. Clinical outcome was demonstrated not to be correlated to cervical sagittal alignment. Likewise, a correlation to the value or change of the OCI was absent.

Chapter 7 describes the results of a systematic review of literature regarding the correlation between Modic changes (MCs) and clinical condition as well as cervical disc degeneration. The prevalence of MCs in cervical spine varied from 5 to 40% and type II was predominant. Patients with MCs were reported to experience more neck pain and neck disability. Cervical disc degeneration was detected more frequently in patients with MCs.

Chapter 8 reports on MCs findings, changes of MCs findings over time and the correlation between MCs findings and neck pain as well as disc degeneration in the cervical spine in our own study cohort. The prevalence of MCs was found to be 18% at baseline and increased to 28% at one year after surgery. Both at baseline and at one-year follow-up, the percentage of patients with and without MCs reporting neck pain was comparable. Likewise, both at baseline and at one-year follow-up, the percentage of patients with and without MCs reporting disabling arm pain was comparable. The patients with MCs demonstrated more radiological degeneration than those without MCs at baseline, but this difference disappeared at one year after surgery. Therefore, in disagreement with literature, we demonstrated only a tendency for

a correlation between the presence of MCs and radiological degeneration, but no correlation to neck pain or disability.

Chapter 9 reports on the occurrence and progression of heterotopic ossification (HO) in patients treated by ACDA, as well as the clinical relevance of HO. The occurrence of HO was 60% at one year, and it increased to 76% at two-year follow-up. 31% of patients was scored as high grade HO at one-year follow-up, and this percentage increased to 50% at two-year follow-up. Clinical outcome does not correlate to HO grade, and no risk factor for high grade HO could be identified. The ROM at the index level was significantly higher in low grade HO group than those patients with high grade HO, but the grade of HO does not consistently correspond to ROM. The McAfee-Mehren classification should be combined with ROM evaluation to properly study HO.

Chapter 10 reports on the occurrence of HO between the two cervical disc prostheses from the NECK and PROCON trial. At two-year follow-up, the occurrence of HO was 68% in patients treated with the activC prosthesis (severe HO 55%), which was comparable with 85% in patients with the Bryan disc (severe HO 44%). The HO progression was similar between the two groups. Clinically, the patients had comparable NDI, physical component summary and mental component summary of SF-36 at two years after surgery, and comparable improvement of clinical outcomes. The ROM of the total cervical spine in the Bryan group (56.4 ± 10.8 degrees) was significantly higher than that in the activC group (49.5 ± 14.0 degrees) at two years after surgery. Therefore, we conclude that the development of HO is independent on the architecture of the cervical disc prosthesis.

NEDERLANDSE SAMENVATTING

Protheses voor het behoud van de mobiliteit van de cervicale wervelkolom na een anterieure discectomie worden regelmatig geimplanteerd. De protheses zijn ontwikkeld om versnelde degeneratie op de belendende niveaux (adjacent segment degeneration; ASD) te voorkomen. De gedachte is dat door behoud van beweging (range of motion; ROM) in de postoperatieve fase, deze ASD wordt beperkt. Het bepleite voordeel van de prothese blijft echter een punt van discussie. Het hoofddoel van dit proefschrift is om inzicht te verschaffen in de relatie tussen behoud van beweeglijkheid en radiologische ASD in patiënten die een cervicale anterieure discectomie op één niveau hebben doorgemaakt. Daarnaast werden andere factoren onderzocht die mogelijk correleren met ASD.

Deze studie is gebaseerd op de NECK en PROCON onderzoeken: twee prospectieve, gerandomiseerde studies waar bij patiënten met cervicale radiculopathie door een uitpuilende tussenwervelschijf (hernia nucleus pulposus; HNP) op één niveau werd gekeken naar het wervel interponaat na verwijderen van de discus. Anterieure cervicale discotomie met prothese (ACDA) werd vergeleken met de conventionele benadering met (ACDF) en zonder 'cage' tussen de wervellichamen (ACD). Na twee jaar follow up werden er geen significante verschillen gevonden in klinische uitkomsten. Dit proefschrift richt zich op de radiologische uitkomsten tussen deze behandelingen.

Hoofdstuk 1 geeft een introductie en de geschiedenis van de chirurgische behandeling van cervicale radiculopathie door een HNP. Op dit moment is ACDF hier voor de gouden standaard vanwege de aangetoonde bevredigende klinische uitkomsten met een laag complicatie risico. Na een ACDF volgt arthrodese van een voorheen beweeglijk niveau en theoretisch kan dit leiden tot verhoogde belasting op de belendende niveaux, wat kan leiden tot versnelde degeneratie op deze niveaux. Dit proces wordt aangeduid als 'adjacent segment degeneration' (ASD). Dit zou kunnen leiden tot meer nekpijn en nieuwe radiculaire klachten op de lange termijn. De cervicale prothese werd ontwikkeld om ASD en daarmee nekpijn en fysieke beperkingen te voorkomen. Echter, de voordelen van het plaatsen van een cervicale prothese worden betwist en de gedachte dat ASD wordt voorkomen door behoud van beweeglijkheid van het geopereerde segment is niet bewezen.

Hoofdstuk 2 beschrijft de resultaten van een 'systematic review' over de effecten van de verschillende cervicale wervelinterponaten na anterieure discectomie die te zien zijn op beeldvorming in de follow up na chirurgie. Een belangrijke bevinding is dat radiologische tekenen van degeneratie op de belendende niveaux (ASD) al bij 50% van de patiënten aanwezig was op baseline. Met een lage graad van waarschijnlijkheid werd gerapporteerd dat op de lange termijn ASD meer voorkwam (10-20%) in de fusiegroep dan in de patientengroep die een prothese ontving. Een belangrijke beperking van dit resultaat is dat dit alleen werd gerapporteerd in een patientengroep die niet alleen bestond uit patienten met een radiculopathie, maar ook uit patienten met een myelopathie.

Hoofdstuk 3 bespreekt de resultaten van de NECK en PROCON patienten. De correlatie tussen de grootte van de hernia en de klachten die patient heeft wordt gerapporteerd. Ook wordt de prognostische waarde van MRI bevindingen gecorreleerd aan de klinische uitkomsten na operatie. Op baseline hadden de patiënten met een 'kleine HNP' een vergelijkbare 'neck disability index' (NDI) en SF-36 ten opzichte van de patiënten met een 'grote HNP'. Op dezelfde manier waren invaliderende armpijn en invaliderende nekpijn vergelijkbaar in de groep met de 'kleine' en de 'grote' HNP. Ook na twee jaar follow up waren er geen verschillen in klinische parameters tussen de twee groepen. Geconcludeerd werd dat bij patienten met een cervicale radiculpathie door een HNP de grootte van de hernia niet met de ernst van de klinische symptomen op baseline correleert en ook niet gebruikt kan worden om de klinische uitkomst twee jaar na operatie te voorspellen.

Hoofdstuk 4 bespreekt de incidentie van radiologische ASD na het plaatsen van een cervicale prothese in vergelijking met cervicale arthrodese. ASD was aanwezig in 34% van de patiënten op baseline en nam toe tot 59% twee jaar na de operatie in de arthrodese groep (ACD en ACDF gecombineerd) en tot 56% in de prothese groep. Progressie van ASD in de twee jaar na operatie was aanwezig in 29% van de patiënten in de arthrodese groep en in 31% van de patiënten in de prothese groep. Hiermee werd aangetoond dat radiologische ASD in de twee jaar na operatie niet wordt voorkomen door het plaatsen van een prothese.

Hoofdstuk 5 bespreekt de relatie tussen ROM van de cervicale wervelkolom (op zowel het geopereerde niveau als van de globale cervicale wervelkolom) en de aanwezigheid van radiologische ASD na cervicale discectomie. In de prothese groep toonde 63% van de patienten met behoud van ROM (> 4 graden op het geopereerde niveau) geen significant lagere incidentie van ASD of minder ASD progressie dan patiënten met een onbeweeglijk cervicaal segment. Onafhankelijk van de chirurgische methode werd er geen correlatie aangetoond tussen ROM en ASD. Ook bestond er geen correlatie tussen behoud van ROM en de NDI. Derhalve is het voordeel van een hulpmiddel om de beweeglijkheid van de nek te behouden en zodoende versnelde degeneratie op de aangrenzende niveaus te verminderen niet bevestigd in dit hoofdstuk.

Hoofdstuk 6 bespreekt de relatie tussen de vorm van sagittale balans van de cervicale wervelkolom en de aanwezigheid van radiologische ASD. Parameters om de sagittale balans van de cervicale wervelkolom te beschrijven waren vergelijkbaar tussen de drie behandelgroepen, zowel op baseline als na twee jaar. Onafhankelijk van de chirurgische methode nam de lordose gedurende twee jaar follow up na operatie C2-C7 toe van 11 tot 13 graden, maar de andere parameters bleven gelijk. Alleen een grote hoek (108 tot 113 graden) tussen achterhoofd en cervicale wervelkolom ('occipitocervicale inclinatie'; OCI) was geassocieerd met de aanwezigheid en progressie van radiologische ASD op zowel baseline als na twee jaar. De klinische uitkomsten waren niet gecorreleerd aan de sagittale balans van de cervicale wervelkolom.

Hoofdstuk 7 beschrijft de resultaten van een systematische literatuur review over zowel de correlatie tussen Modic veranderingen (MCs) en de klinische conditie als ook de correlatie tussen MC en degeneratie van de cervicale tussenwervelschijf. De prevalentie van MCs in de cervicale wervelkolom varieerde van 5 tot 40% waarbij type II het meest voorkwam. Patiënten met MCs ondervonden meer nekpijn en fysieke beperking van de nek. Ook degeneratie van de cervicale tussenwervelschijf werd vaker gezien in patiënten met MCs.

Hoofdstuk 8 bespreekt bevindingen uit de NECK en PROCON trials over MCs, veranderingen in MCs gedurende follow up en de correlatie tussen MCs en enerzijds nekpijn en anderzijds degeneratie van de cervicale tussenwervelschijf. De prevalentie van MCs was 18% op baseline en nam toe tot 28% één jaar na de operatie. Op zowel baseline als één jaar na operatie was het percentage patiënten met en zonder MCs die klachten van nekpijn hadden vergelijkbaar. Op dezelfde manier was het percentage patiënten met en zonder MCs die klachten hadden van invaliderende armpijn vergelijkbaar op zowel baseline als na één jaar. Op baseline hadden de patiënten met MCs meer radiologische degeneratie van de tussenwervelschij dan de patiënten zonder MCs, maar dit verschil was één jaar na de operatie niet meer aanwezig. Derhalve, in tegenstelling tot de literatuur, laat ons onderzoek alleen een tendens zien voor een correlatie tussen de aanwezigheid van MCs en radiologische degeneratie, maar geen correlatie met nekpijn of fysieke beperking.

Hoofdstuk 9 bespreekt het vóórkomen en progressie van heterotope ossificatie (HO) in patiënten behandeld met een prothese als ook de klinische relevantie van HO. HO kwam in 60% van de patienten voor na één jaar follow up en nam toe tot 76% na twee jaar follow up. Bij 31% van de patiënten werd HO beoordeeld als hooggradig en dit percentage nam toe tot 50% na twee jaar. De klinische uitkomst correleert niet met de HO gradering en er kon ook geen risicofactor voor hooggradig HO gevonden worden. De ROM op het geopereerde niveau was significant hoger in de laaggradige HO groep dan in patiënten met hooggradig HO, maar de HO graad komt niet consequent overeen met de ROM. Geconcludeerd kan worden dat de radiologische McAfee-Mehren classificatie moet worden gecombineerd met de bepaling van de range of motion van het betreffende segment om de klinische implicaties van HO adequaat te kunnen beoordelen.

Hoofdstuk 10 bespreekt het vóórkomen van HO bij de twee cervicale tussenwervelschijf protheses uit de NECK en PROCON studies. Na twee jaar kwam HO voor in 68% van de patiënten die behandeld waren met de activC prothese (55% ernstige HO) en was vergelijkbaar met de 85% HO bij de patiënten met de Bryan discus (44% ernstige HO). De HO progressie was vergelijkbaar tussen de twee groepen. Klinisch gezien hadden de patiënten vergelijkbare NDI, PCS en MCS twee jaar na de operatie en vergelijkbare verbetering van de klinische uitkomsten. De ROM van de gehele cervicale wervelkolom in de Bryan groep (56.4 ± 10.8 graden) was significant hoger dan in de activC groep (49.5 ± 14.0) twee jaar na de operatie; dit beoordeelden we echt niet als klinisch relevant. Derhalve concluderen we dat het beloop van HO onafhankelijk is van het ontwerp van de cervicale tussenwervelschijf prothese.

CURRICULUM VITAE

Xiaoyu Yang was born on February 21st, 1990 in Chifeng, P.R. China. After graduating from high school, he started medical school in 2008 at Henan University of Science & Technology in Luoyang, P.R. China.

In 2013, Xiaoyu graduated from medical school and obtained the bachelor's degree of Clinical Medicine (M.D.). He was then selected to participate in a special program for medical students organized by Jilin University and the First Hospital of Jilin University in Changchun, P.R. China. This program enabled him to combine a master's degree of Clinical Medicine with the surgery residency program. During this program, he received his initial academic training in clinical research as well as surgical training focused on neurosurgery. In 2014, he was certified and registered as a surgeon in P.R. China. He was awarded the Graduate Scholarship for the whole three academic years. In 2016, he successfully obtained the master's degree of Clinical Medicine (M.Sc.) and accomplished his surgical residency training.

Subsequently, he started the research described in this thesis in the department of Neurosurgery at Leiden University Medical Centre (supervisors: Prof. dr. W.C. Peul and Dr. C.L.A. Vleggeert-Lankamp) with a Ph.D. scholarship awarded by China Scholarship Council. In the winter of 2017, he participated in the International Physician Observer Program in Cleveland Clinic in Cleveland, USA (supervisor: Prof. Edward Benzel). In the summer of 2018, he was awarded the Erasmus grant from the European Union, to study in the department of Neurosurgery at Sheffield Teaching Hospitals in Sheffield, UK (supervisor: Dr. Marcel Ivanov). In December 2018, with the Leiden University Fund, he presented his research during Cervical Spine Research Society 46th Annual Meeting in Arizona, USA. In March 2019, he attended Cervical Spine Research Society Asia Pacific section 10th Annual Meeting in Yokohama, Japan and presented his research during the conference. In May 2019, he was granted the Mario Boni Award during the Cervical Spine Research Society Europe 35th Annual Meeting in Rome, Italy. In June 2019, he was granted Cultural Foundation Grant from Prins Bernhard Cultural Foundation to support his further research in the University of Cambridge in the UK.

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