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PII: S1529-9430(22)01015-4
DOI: https://doi.org/10.1016/j.spinee.2022.11.006
Reference: SPINEE 58817

To appear in: *The Spine Journal*

Received date: 14 July 2022
Revised date: 3 November 2022
Accepted date: 8 November 2022

Please cite this article as: Caroline M.W. Goedmakers , Floor de Vries , Lisette Bosscher , Wilco C. Peul , Mark P. Arts , Carmen L.A. Vleggeert-Lankamp , Long-term results of the NECK trial: implanting a disc prosthesis after cervical anterior discectomy cannot prevent adjacent segment disease. 5-years clinical follow-up of a double-blinded randomised controlled trial, *The Spine Journal* (2022), doi: https://doi.org/10.1016/j.spinee.2022.11.006

Long term results of the NECK trial: implanting a disc prosthesis after cervical anterior discectomy cannot prevent adjacent segment disease *5-years clinical follow-up of a double-blinded randomised controlled trial*

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Funding: Grant BBraun Medical (F, paid directly to institution)
Grant CSRS-Europe (F, paid directly to institution)

Trial registration: Dutch Trial Register Number: NTR1289

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Abstract

Background Context: Motion preserving anterior cervical disc arthroplasty (ACDA) in patients with cervical radiculopathy was introduced to prevent symptomatic adjacent segment disease as compared to anterior cervical discectomy and fusion (ACDF).

Purpose: To evaluate the long-term outcome in patients with cervical radiculopathy due to a herniated disc undergoing ACDA, ACDF or ACD (no cage, no plate) in terms of clinical outcome measured by the Neck Disability Index (NDI). Likewise, clinically relevant adjacent segment disease is assessed as a long-term result.

Study design: Double-blinded randomized controlled trial

Patient sample: One hundred-nine patients with one level herniated disc were randomized to one of the following treatments: ACDA, ACDF with intervertebral cage, ACD without cage.

Outcome Measures: Clinical outcome was measured by patients' self-reported NDI, Visual Analogue Scale (VAS) neck pain, VAS arm pain, SF36, EQ-5D, perceived recovery and reoperation rate. Radiological outcome was assessed by radiographic cervical curvature and adjacent segment degeneration (ASD) parameters at baseline and up until five years after surgery.

Methods: To account for the correlation between repeated measurements of the same individual Generalized Estimated Equations (GEE) were used to calculate treatment effects, expressed in difference in marginal mean values for NDI per treatment group.

Results: Clinical outcome parameters were comparable in the ACDA and ACDF group, but significantly worse in the ACD group, though not reaching clinical relevance. Annual reoperation rate was 3.6% in the first two years after surgery, declined to 1.9% in the years thereafter. The number of reoperations for ASD was not lower in the ACDA group, while the number of reoperations at the index level was higher after ACD, when compared to ACDF and ACDA.

Conclusions: A persisting absence of clinical superiority was demonstrated for the cervical disc prosthesis five years after surgery. Specifically, clinically relevant adjacent level disease was not prevented by implanting a prosthesis. Single level ACD without implanting an intervertebral device provided worse clinical outcome, which was hypothesized to be caused by delayed fusion. This stresses the need for focusing on timely fusion in future research.

Keywords: Cervical discectomy; cervical radiculopathy; prosthesis; neck disability index; radicular pain; adjacent segment disease

Introduction

In the treatment of cervical radiculopathy due to a herniated disc, the anterior approach to decompress the spinal nerve root via a discectomy is the most commonly performed surgical intervention. An universally used method, to bridge the gap created by the discectomy, is to graft it using a cage which eventually facilitates bony fusion. Theoretically, fusion increases the stress-load on the adjacent disc levels which can cause pain and decrease in functionality on the short term, and recurrent nerve compression on the long-term (adjacent segment disease; ASD). The cervical disc prosthesis was introduced to keep the index level mobile and to avoid ASD.

Previous observational studies evaluating the short-term outcome of anterior discectomy with a cage (ACD Fusion) or with a prothesis (ACD Arthroplasty) in radiculopathy patients reported only minimal, though not clinically relevant, differences between the two interventions [1]. Likewise, the RCTs on this subject, evaluating the two-year results, could not discern a clinically relevant difference; neither in neck disability index, nor arm pain [2, 3, 4, 5, 6]. Although implanting a prosthesis did not provide superior clinical outcome in the short term, long-term data could provide different results. Adjacent segment disease has long been a radiographic diagnosis and was typically reported to occur in the middle to long-term follow-up [7]. Clinical relevance, however, is reflected in new radiculopathy symptoms, corresponding to degenerative radiographic changes, on the level adjacent to the index level surgery that require reoperation [8].

It is therefore relevant to study long-term results in patients undergoing anterior discectomy to treat cervical radiculopathy. We previously reported the two-year clinical and radiological results of the NECK trial, in which patients were randomized to be subjected to ACD, ACDF or ACDA, and demonstrated no

differences in clinical outcome between the three groups. In the current study we report the outcomes five years after surgery [3]. The clinical condition of patients is evaluated to assess the long-term effect of the interventions, including the reinterventions at the index level, and to appraise the incidence of adjacent segment disease by scoring the reoperations at the adjacent levels.

In the NECK trial a third treatment arm was included, in addition to the evaluation of alleged superiority of the prosthesis over fusion, in which clinical outcome of ACD was assessed. The two-year data on ACD did not deviate from ACDF and ACDA outcome, but in the current study it is evaluated whether this equivalence persists after longer follow-up.

Materials and methods

A prospective, randomized double-blinded multicenter trial was conducted among patients with cervical radiculopathy due to single level disc herniation (NEtherlands Cervical Kinematics, or NECK, trial). Patients were randomly assigned, using a computer, into three groups: anterior cervical discectomy with disc prosthesis (ACDA), anterior cervical discectomy with cage (ACDF) and anterior cervical discectomy without cage (ACD). Both patients and research nurses, evaluating clinical outcome, were blinded to the allocated treatment. The protocol was approved by the Central Medical Ethics Committee XXX ("Commissie Medische Ethiek XXX University Medical Center," decision letter P08.011) and the board of directors of the XXX hospital XXX, XXX, XXX Medical Center and XXX, including an approval for randomization after anesthetic induction, in agreement with the Central Ethics Committee XXX. The protocol was also approved by the "Medical Ethics Committee XXX" for the Medical Center XXX (M08-038). Written informed consent was obtained

from all patients. The design and study protocol were previously published [9]. XXX Trial Register Number: NTR1289.

Eligibility and randomization

Patients (aged 18 to 65 years old) with radicular signs and symptoms, in one or both arms (pain, paresthesia or paresis in a specific nerve root distribution), for at least eight weeks and for whom conservative therapy (no physiotherapy or injections were prescribed) 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 an accompanying 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. At the time of enrollment an independent research nurse verified the persistence of the symptoms. Patients with previous cervical surgery (either anterior or posterior), absence of motion, increased anteroposterior translation, very narrow (< 3 mm) intervertebral space, severe segmental kyphosis (> 3 degrees) at the index level on static or dynamic X-rays, neck pain only or symptoms and signs of myelopathy were excluded. Furthermore, patients with metabolic and bone diseases (osteoporosis, severe osteopenia), neoplasm or trauma of the cervical spine, spinal anomaly (Klippel Feil, Bechterew, OPLL) or severe mental or psychiatric disorders were excluded.

A randomized design with variable block sizes was used (computer-assisted) in a 1:1:1 ratio, with allocations stratified by center. Allocations were stored in prepared opaque, coded and sealed envelopes. The key was only accessible to the ProMISe data management system of the Department of Medical Statistics and BioInformatics of the XXX University Medical Center. All patients gave

informed consent. After induction of anesthesia, the prepared envelope was opened and patients were randomly allocated to one of the treatment arms. Patients, the nursing department and research nurses remained blinded to the treatment group during a follow-up of two years. At two-years follow-up patients were unblinded.

Disc Prosthesis

The investigational device used in the ACDA group was the Activ®C flat artificial cervical disc (Aesculap AG, Tuttlingen, Germany). The Activ®C device is composed of two flat Cobalt-Chrome-Molybden alloy metal endplate components with spikes on the superior endplate, an inferior endplate and a keel for primary stability. The inferior prosthesis plate has an integrated polyethylene inlay. The implants are available in six different sizes (XS, S, M, L, XL and XXL) and in three heights (5, 6, and 7 mm).

Interventions

All patients were in the supine position with their neck slightly extended under general anesthesia. The affected cervical disc level was identified using fluoroscopy. A small transverse incision was made either on the right or left side depending on the surgeon's preference. Medial to the carotid sheath, the prevertebral space was opened, and the anterior cervical spine was exposed. Caspar spreader and two distraction pins were placed in the affected segment. Care was taken to not damage the adjacent level discs. A standard anterior discectomy, using loupe magnification or microscope (depending on the surgeon's preference), was performed in all cases. The posterior longitudinal ligament was opened, and the nerve root and dura were decompressed

adequately. If required, a vacuum drain was left behind and the wound was closed in layers.

For patients randomized to the ACD group, no intervertebral device was placed: the procedure was solely a discectomy without fusion. The disc was removed, endplates were 'scrubbed' and vertebra were presumed to fuse. In patients randomized to the ACDF group, an interbody PEEK cage, either filled with synthetic bone substitute or autologous bone (chips locally harvested), was placed within the intervertebral space under fluoroscopic guidance. No plate or integral fixation was used. The brand of cage depended on the surgeons' preference and daily practice. A total of three different brands were used between all included patients. For patients randomized to the ACDA group, special attention was given to the placing of the distraction pins in the adjacent levels. With anteroposterior fluoroscopy, the mid-vertebral body position was ensured. After decompression of dura and nerve roots, the implant size and height were determined and the endplates were prepared for proper fitting of the Activ®C flat prosthesis, including preparing a sleeve for the keel to fit in. The device was inserted under slight distraction and fluoroscopic guidance. Postoperatively, all patients were encouraged to mobilize as soon as possible. No collars were prescribed.

In all participating centers, one senior surgeon with advanced training in cervical spine surgery was trained to implant the prosthesis. After implanting ten prostheses, the surgeon was allowed to implant prostheses for the RCT. Four of the participating hospitals referred their patients for surgery to the main referral hospital (XXX), where patients were operated on by one trained surgeon dedicated to this trial. Overall, three surgeons in three hospitals were responsible for the implantation of the prostheses (16, 29 and 64 interventions per center).

Clinical outcome measures

The primary outcome measure was the Neck Disability Index (NDI). The NDI is a 10-item questionnaire on three different aspects; pain intensity, daily work-related activities and non-work 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 100-point scale (50 points = 100 points). 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, 11, 12].

Secondary outcome measures were the Visual Analogue Scale for arm pain (VAS arm) and for neck pain (VAS neck), the EuroQol quality of life questionnaire, including a Visual Analogue Scale for health (VAS health), the Likert patient perceived recovery scale, and the Medical Outcome Study 36-item short-form Generated Health Survey(SF 36). The 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 [13].

The EuroQol (EQ-5D) measures five dimensions (mobility, self-care, daily activities, pain/discomfort, anxiety/depression), on a three-point scale (no, some, or extreme problems).
Whereas the EQ-5D provides society's valuation for the patients' health, the patients themselves will also provide their own valuations for their health on a visual analogue scale, ranging from 0,0 (as bad as death) to 1,0 (optimal health).

The 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 [14]. “Complete recovery” and “almost complete recovery” are defined as a good result, which was used to dichotomize the data. A Likert perceived recovery evaluation was performed for recovery of global health and recovery of arm pain separately.

The SF36 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 [15, 16, 17]. The PCS and 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.

All outcome scores were assessed at baseline, at 2, 4, 8, 12, 26, 52, 104 and 260 weeks, except for the Likert perceived recovery score which was not evaluated at baseline. In the first year after surgery patients follow-up was evaluated with the help of research nurses, that could assist in filling in the questionnaires. Thereafter, questionnaires were sent to the patients and their scores were inputted in the study database by a data manager. At five-years follow-up all patients were contacted by phone to encourage them to fill in the questionnaires and to give them information on the radiological follow-up. Patients were specifically queried for reoperations in the cervical area.

Radiological outcome measures

Flexion-extension radiographs of the cervical spine were obtained at baseline and after 1, 2, and 5 years. To evaluate cervical spine curvature, a line was

drawn along the posterior side of the vertebra from the posterior inferior part of C2 to the posterior superior part of C7. If a part of the vertebral body of C3 to C6 crossed this line, the cervical spine was considered to be kyphotic, if the bodies were arranged along this line, the cervical spine was considered to be straight, and if the bodies of the vertebrae remained anterior of the line, the cervical spine was considered to be lordotic

If patients needed reoperation, a distinction was made between reoperation at index level or reoperation for ASD. If patients required reoperation for new radiculopathy symptoms corresponding to degenerative radiographic changes on the level adjacent to the index level surgery, as assessed by two independent reviewers, they were classified as ASD reoperations.

Sample size

The sample size calculation was based on the hypothesis that the average NDI two years after ACDA is superior to the average NDI after anterior discectomy with or without interbody fusion. Details on this calculation can be found in the two-years results publication [3].

Statistical Analysis

Groups were compared based on an intention-to-treat analysis. Differences between groups at baseline were tested. Differences between groups at all follow-up points (2, 4, 8, 12, 26, 52, 104 and 260 weeks) were analyzed with repeated measurement analysis. To account for the correlation between repeated measurements of the same individual, treatment effects, expressed in difference in marginal mean values for NDI, were calculated using Generalized Estimating Equations (GEE).

At the moment of randomization, the study was stratified by the administrative center for the purpose of analyzing possible heterogeneity among centers and attempting a clinical interpretation of such heterogeneity. Those centers that were referring patients to the same hospital and same surgeon for treatment were combined. Hence, for the purpose of the analysis of heterogeneity, a center means the actual location where the treatment (according to random allocation) took place.

We defined a 20-point lower NDI score (on a 100 point scale) as a clinically relevant benefit to justify ACDA. This value was decided based upon the assumption that superiority would be convincing enough to change the surgical guidelines [18].

Data collection and quality assurance was performed with the ProMISe data management system of the Department of Medical Statistics and BioInformatics of the XXX University Medical Center. IBM SPSS software, version 22.0, was used for all statistical analyses.

Results

Between October 2010 and July 2014, 156 consecutive patients with cervical radiculopathy, due to a herniated disc, were eligible for inclusion. 44 patients declined participation and 112 patients signed informed consent and were enrolled in the NECK Trial (Figure 1). Three patients were excluded because baseline data was missing.

The included 109 patients were randomly assigned to; ACD (38 patients), ACDF (36 patients) or ACDA (35 patients). No cross-over occurred. There were no significant differences in baseline characteristics between the three treatment arms (Table 1). At five-years follow-up, data on clinical outcome

measures was available for 89 out of 109 patients (82% compliance rate) (Figure 1). One patient died during follow-up due to causes unrelated to the study. Data on additional surgery on the cervical spine was retrieved from 107 patients (1 patient changed phone numbers and could not be contacted). Data on complications, operating time, blood loss and hospital stay have been previously reported [3].

Clinical outcome measures

All outcome measures improved after surgery, regardless of the treatment strategy (Table 2). The NDI decreased significantly from 41-47 points at baseline to mean values between 18 and 21 one year after follow-up and remained at this low level up to five years after surgery. However, after five years NDI increased to 24 ± 23 in the ACD group, as compared to a decline to 13 ± 15 and 15 ± 14 in the ACDF and ACDA group, respectively ($p = 0.052$; Figure 2). Treatment effects were calculated using estimated marginal means from the mixed model analysis and demonstrated small differences in NDI ranging from 3.5 - 8.6 on a 100 point NDI scale (Table 3). Additionally, the maximal possible differences between the individual treatment strategies revealed that the maximum possible differences in outcome of NDI between ACD and ACDA ranged from -17.2 to - 0.2 on a 100-point scale. Although this difference did not exceed the minimal clinically important difference (MCID) of 20 points on the 100-point NDI scale, it reached statistical significance ($p = 0.05$).

The VAS arm pain improved significantly from 57-64 mm before surgery to 16-24 after one year in all treatment arms and remained at this value at five-years follow-up. There was no significant difference in improvement of VAS arm pain among the three surgical interventions (Table 2, Figure 3).

The VAS neck pain demonstrated a similar pattern as the VAS arm pain, with comparable reduction of neck pain in all treatment arms after one, two and five years without significant differences among the groups (Table 2, Figure 4). Quality of life, measured by the EQ-5D, VAS health, Likert global health and Likert arm pain improved after surgery, however values for the ACDF group tended to be better, whereas values for the ACD group tended to be inferior, reaching statistical significance in EQ-5D and perceived arm pain recovery ($p = 0.015$) (Table 2). At five-years follow-up an inconsistency was found comparing Likert perceived arm pain recovery, that was only scores positive in 50% of patients in the ACD group ($p = 0.015$), while the mean VAS arm pain decreased from 64 at baseline to 25 after five years in the ACD group and was not significantly different from the values in the ACDF or ACDA group (Table 2).

SF-36 baseline scores started around 40 and 30 (out of 100) for PCS and MCS respectively at baseline and remained around these values throughout follow-up, without statically significant differences between treatment groups (Table 2).

Radiological outcome measures

Kyphosis

At baseline a lateral standing X-ray was available for 93 patients to evaluate cervical curvature. For 11 patients, baseline X-rays were missing, but X-rays made within three months after surgery were available. Therefore, for 104 patients, baseline information on the shape of the cervical spinal column in neutral position was available. 54 patients demonstrated a lordotic spine, 41 patients had a straight spine, and seven a kyphotic spine. At two-years follow-up 96 patients had X-rays available. Most of the patients that had a lordotic or straight spine at baseline remained lordotic or straight; only one patient

developed a kyphotic spine, but this reshaped to a straight spine on the five-years follow-up X ray. After five years 64 patients had X-rays available (Table 4). In the patient group with a kyphotic cervical curvature at baseline, only one patient remained kyphotic, even at five-years follow-up; the other six patients had recovered to a straight or lordotic spine at two-years follow-up. One of those patients (that had received ACD) recovered to a lordotic spine after five years. The number of patients with a kyphotic spine was deemed too small to make a meaningful correlation to clinical data.

Reoperations

At two-years follow-up, seven out of 98 patients were re-operated; four at index level (1 ACDF, 1 ACDA, 2 ACD) and three at the adjacent level (1 ACDF and 2 ACDA). During the three years thereafter, another five out of 89 patients were reoperated; two at index level (2 ACD) and three at the adjacent level (2 ACDF and 1 ACDA). Overall annual reoperation rate was 3.6% in the first two years, but declined to 1.9% in the three years thereafter.

In summary, after five years of follow-up six patients were reoperated for new radiculopathy symptoms corresponding to degenerative radiographic changes on the level adjacent to the index level surgery (ASD) (3 ACDF, 3 ACDA). Average annual reoperation rates for ASD are reported per treatment group in Table 5 and compared to annual reoperation rates for other studies with similar follow-up.

The other six patients were reoperated at the index level (1 ACDF, 1 ACDA, 4 ACD). The ACDA patient from the latter group had persisting complaints of neck pain after having received a prosthesis. The pain was related to neck movements and subsequently the level was immobilized by adding a plate to the index level; complaints, however, persisted. Average annual reoperation rates at

index level are reported per treatment group in Table 6 and compared to annual reoperation rates for other studies with similar follow-up.

Discussion

The objective of the NECK trial was to evaluate whether implanting a prosthesis would provide superior clinical outcome after anterior discectomy [9]. During an anterior discectomy the cervical spinal root is decompressed in order to relieve radicular symptoms in the arm. The additional short-term purpose of a prosthesis is to mimic the non-degenerated mechanics of the cervical spine segment and therefore decrease disability of the neck after surgery. It was hypothesized ACDA would demonstrate clinical superiority in a 20-point lower score on NDI (100 points scale), as compared to ACDF and ACD. We previously demonstrated that at one and two years after surgery NDI was comparable between the three groups [3]. In this follow-up study it is demonstrated that, persistently five years after surgery, the prosthesis does not provide superior NDI scores compared to fusion. This result is in agreement with previous long-term double-blinded RCTs [8] [19] [20], although one of the RCTs on this topic presents different results [21]. Zigler et al. reported a significant decrease in VAS neck pain in favor of the prosthesis, which they claimed to be clinically relevant (10 mm difference). However, this study did not find a difference in NDI. They focused on the lower reoperation rate in the prosthesis group in particular, which was lower at the adjacent and index level in the ACDA group (Table 5 and 6) [22].

The hypothesized long-term advantage of a prosthesis is to avoid adjacent level disease. By fusing a segment, mechanical stress on the adjacent levels is increased, which potentially triggers accelerated degeneration at these levels. This may subsequently initiate recurrent radicular complaints. If new radicular

complaints are invalidating to an extent that a surgical intervention is needed, they are deemed to be clinically relevant. Evaluating the reoperations for adjacent level radicular complaints is considered to be a suitable tool to evaluate clinically relevant adjacent level disease [8]. In this study three patients were operated on an adjacent level within two years after surgery, and an additional three patients were operated in the subsequent three years. Three of these six patients were initially subjected to ACDF and three to ACDA. These results suggest that implanting a prosthesis does not prevent adjacent level disease. Presumably, this is due to the preceding observation that a prosthesis loses its full range of mobility in the first years after implanting due to heterotopic ossification (HO) [23], which is in agreement with the observations of other authors [24] [25]. We concluded that HO was present in 76% of patients after two years of follow-up and that it interfered with range of motion at the index level: namely, the range of motion was less in patients with higher grades of HO. This percentage is in agreement with the 63% prevalence of grade III and IV HO four years after implanting a prosthesis by Suchomel [25]. Surgical outcomes may vary by technique and surgical experience; implants do play a role, however, there is currently no literature available finding statistically significant differences in clinical outcomes after surgery, between different brands of instrumentation. Therefore, the comparison between the PEEK cages and the Activ®C prosthesis in this study was deemed to be valid, even though three different types of PEEK cages were used.

A frequently cited annual incidence of ASD after fusion is 2.9% [7], though more recent studies report substantially lower rates in comparing ACDA to ACDF (Table 5), which are in agreement with the results presented in the current study. It is noteworthy however, that our results illustrate that the annual reoperation rate decreases over time. Particularly in patients that are included in an RCT, who have more frequent follow-up visits and who have a higher

chance to be subjected to a non-standardized treatment regimen, the surgeon is prone to reoperate if the patient has persisting or recurrent complaints. This may explain the difference in overall annual reoperation rate from 3.6% in the first two years to 1.9% in the subsequent three years. This phenomenon was also reported in the 10-years data of a Swedish RCT on this topic [26]. In this study no further analysis was performed (what the index level was, and whether ASD occurred inferiorly or superiorly) on the six patients that had to be reoperated for ASD, as the numbers were deemed too low to draw meaningful conclusions. However, in future studies the analysis of larger groups of patients undergoing reoperation for ASD, potentially retrospectively, may provide more insight into the etiology of ASD.

Another notable result is that clinical outcome for ACD patients tended to be worse than for ACDF and ACDA patients. A Cochrane review comparing ACD to ACDF reported low and very low quality evidence that there was no significant difference in short-term pain relief and Odom's criteria (based on two RCTs) [27]. However, in this long-term follow-up study we demonstrated that in the ACD group; neck disability, EQ-5D, and perceived arm pain recovery were worse five years after surgery. The difference reached statistical significance, even though the MCID was not reached. Differences between ACDA and ACDF groups did not meet statistical significance, nor clinical relevance (MCID). Anterior discectomy without an intervertebral device is not regularly performed, as it is presumed to induce kyphosis of the cervical column and as a consequence induce neck pain. This hypothesis could not be confirmed in the Cochrane review that presented data in agreement with our study, and that contradicts the occurrence of kyphosis five years after ACD [27]. Another argument that could be raised against ACD is that it causes a relative decrease in foraminal height which could potentially cause recurrent compression of the nerve root. However, mean foraminal height was only slightly decreased in the

ACD group, and foraminal height did not correlate to radicular symptoms nor to general clinical outcome [28].

We hypothesize that fusion is delayed in the ACD group, in agreement with observations summarized in the Cochrane review [27]. If an intervertebral device is placed, this leads to immobilization of the vertebra, which stops the induction of osteophyte growth. However, if the vertebrae are allowed non-physiological movement (as is the case in ACD), even though it is minimal, this may allow osteophytes to grow, resulting in recurrent irritation of the nerve root. This would lead to more reoperations at the index level, which is indeed the observation in the current study. Figures on reoperations on the index level in other long-term RCTs demonstrate varying rates, but do not contradict our findings (Table 6). In our study, six patients were reoperated at the index level, of which four from the ACD group. It has to be noted, however, that the surgical incentive to reoperate is low after ACD, since this technique deviates from the normal routine in which an ACDF is performed. Interestingly, the number of reoperations at index level was not higher in the ACDA group, though the index level remained mobile too in this group. Presumably, the mobility allowed by the prosthesis was capable of mimicking a physiological movement.

Our study has several strengths. The compliance rate was high, with 82% of patients completing the PROM questionnaires after 5 years. Furthermore, the study was double-blinded, allowing the type of procedure performed to be unknown to patients and research nurses up until two years after surgery. However, this study also has limitations, in addition to the aforementioned variation induced by surgical technique, experience and implants, as well as the lacking of an analysis on location of ASD in relation to the index surgery; the number of patients included was limited and the power calculations were not based on several of the evaluated outcomes. Moreover, radiological

degenerative changes were not separately assessed but only when deemed clinically relevant by needing reoperation. Furthermore, the length of follow-up for studies evaluating ASD is always a limiting factor, as the incidence of ASD increases with longer follow-up [7].

In conclusion, our long-term results demonstrate, in addition to a persisting absence of clinical superiority of the cervical disc prosthesis, that clinically relevant adjacent level disease occurs after cervical anterior discectomy, and that it cannot be prevented by implanting a disc prosthesis. This study also illustrates that ACD provides less favorable clinical results long-term, which is presumably caused by a delay in fusion of the segments. This stresses the importance of achieving timely fusion after anterior discectomy and therefore future research should focus on that aspect of the procedure.

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Legends to the figures and tables

Figure 1:

Overview of patients enrollment

One hundred fifty-six were willing to consider participating in the study, 44 patients declined participation after the initial approach, and 112 patients signed informed consent. For 3 patients, baseline data was missing, so these were excluded from evaluation. The remaining 109 patients were randomly assigned to ACD (38 patients), ACDF (36 patients) or ACDA (35 patients). At five years follow-up there was an 82% compliance rate of patients that filled in the questionnaires: ACD (30 patients), ACDF (32 patients) and ACDA (27 patients).

Figure 2:

Neck Disability Index values during follow-up

NDI: Value for intake for all three groups was set at the mean value of NDI at intake (co-variate in GEE analysis) because there were no significant differences between the groups at baseline. There were no significant differences between the three groups. All three groups reach comparable values after two years, although the patients in the ACD group tended to demonstrate a less favorable outcome in NDI.

Figure 3

VAS arm pain values during follow-up

VAS arm pain: patients in the three groups demonstrate a decline in VAS arm pain shortly after surgery. There were no significant differences between the three groups. In the ACD group, there is a tendency to an increase in arm pain at five years.

Figure 4

VAS neck pain values during follow-up

VAS neck pain: patients in all three treatment arms drop in VAS neck pain shortly after decompressive surgery. There were no significant differences between the three groups. In agreement with the curves demonstrated for VAS arm pain, the values for VAS neck pain in the ACD group demonstrate a tendency to increase at five-years follow-up.

Table 1

Patient demographics.

Baseline characteristics of all patients in the ACD, ACDF and ACDA group. No statistical significant differences were present between the three groups, with the exception of the Body Mass Index. This was significantly smaller in the ACD group. Running BMI as a co-variate in the GEE analysis did not result in a significant influence of BMI on NDI (p=0.148).

Table 2

Clinical outcome at baseline, after one year, two and five years of follow-up. P-values for the between-treatment comparisons are given for each time point,

calculated using the ANOVA test for continuous data and the Chi-Squared test for binary data in SPSS. Only in the EQ-5D statistically significant differences at baseline existed between the three treatment arms: the patients in the ACDF group had a significantly higher baseline score.

Table 3

Treatment effects of ACD, ACDF and ACDA at five-years follow-up. Corrected for pre-operative NDI score. The treatment effects are the differences in estimated marginal means between groups computed with a linear mixed model.

Table 4

Radiological outcome: Cervical curvature at baseline and evolution during follow-up. The number of patients per evaluation time point was 104 at baseline, 96 at two years follow-up, and 64 at five-years follow-up. FU = follow-up.

Table 5

Annual reoperation rates at the adjacent level retrieved from RCTs comparing ACDF, ACDA, ACD.

Table 6

Annual reoperation rates at the index level retrieved from RCTs comparing ACDF, ACDA and ACD.

Table 1

	ACD	ACDF	ACDA
Age (years; mean ± SD)	46.4 ± 7.3	47.5 ± 8.0	46.5 ± 8.7
Body Mass Index (mean ± SD)	25.4 ± 3.6	27.6 ± 5.4	27.0 ± 3.7
Sex			
Male	20	14	17
Female	18	22	18
Smoking			
Never	21	20	21
Occasionally	1	3	1
Regularly	16	13	13
Level HNP			
C5C6	19	19	19
C6C7	19	16	16
C7T1	0	1	0
Duration of complaints (weeks, mean ± SD)	36.9 ± 53.5	55.4 ± 90.4	44.2 ± 64.3
Baseline NDI	54.5 ± 12.7	51.2 ± 10.7	55.5 ± 14.0
Baseline VAS	56.5 ± 31.3	52.8 ± 25.8	49.6 ± 27.2

Table 2

	Baseline	1-year FU	2-year FU	5-year FU
NDI				
ACD	45 ± 16	21 ± 16	19 ± 15	24 ± 23
ACDF	41 ± 13	18 ± 17	19 ± 18	13 ± 15
ACDA	47 ± 17	18 ± 18	20 ± 22	15 ± 14
p-value	.294	0.670	.929	.052
VAS arm pain				
ACD	64 ± 22	24 ± 31	18 ± 25	25 ± 32
ACDF	57 ± 20	18 ± 26	15 ± 23	13 ± 22
ACDA	60 ± 24	16 ± 19	17 ± 30	14 ± 21
p-value	.331	.424	.880	.184
VAS neck pain				
ACD	53 ± 27	24 ± 27	21 ± 23	29 ± 32
ACDF	53 ± 26	28 ± 28	23 ± 27	19 ± 24
ACDA	50 ± 27	17 ± 19	23 ± 32	17 ± 25
p-value	.849	.172	.934	.168
EQ-5D				
ACD	0.43 ± 0.28	0.83 ± 0.20	0.81 ± 0.22	0.75 ± 0.30
ACDF	0.64 ± 0.24	0.82 ± 0.20	0.81 ± 0.23	0.90 ± 0.13
ACDA	0.51 ± 0.28	0.83 ± 0.20	0.80 ± 0.28	0.87 ± 0.14
p-value	.004	.978	.989	.015
VAS health				
ACD	48 ± 26	71 ± 23	69 ± 24	65 ± 28
ACDF	53 ± 23	76 ± 22	74 ± 24	78 ± 21
ACDA	45 ± 22	72 ± 21	74 ± 25	73 ± 21
p-value	.336	.627	.663	.109
Likert; global health (%)				

ACD		52.9	62.5	56.7
ACDF		77.1	67.6	75.0
ACDA		61.8	65.6	66.7
p-value		.105	.907	.312
Likert; arm pain (%)				
ACD		58.8	68.8	50.0
ACDF		77.1	73.5	81.3
ACDA		67.6	65.6	77.8
p-value		.264	.781	.015
Physical component score (PCS)				
ACD	40 ± 6	44 ± 5	44 ± 6	44 ± 7
ACDF	41 ± 5	45 ± 7	44 ± 7	45 ± 6
ACDA	39 ± 7	44 ± 5	43 ± 7	45 ± 5
p-value	.316	.949	.614	.874
Mental component score (MCS)				
ACD	29 ± 6	32 ± 7	32 ± 6	31 ± 7
ACDF	30 ± 7	34 ± 5	34 ± 6	34 ± 5
ACDA	29 ± 8	32 ± 6	34 ± 7	31 ± 7
p-value	.913	.197	.293	.060

Table 3

	Treatment effect	**Minimal treatment effect (95% CI)**	**Maximal treatment effect (95% CI)**	**p-value**
ACD vs. ACDF	-5,132	-12,994	2,731	,201
ACD vs. ACDA	-8,587	-17,158	-,016	,050
ACDF vs. ACDA	-3,455	-10,938	4,027	,365

Table 4

Baseline	**Follow up**	**Number of patients at 2 yr FU**	**Change from 2 to 5 yr FU (n=64)**
Lordosis	Lordosis	44	Lordosis to straight ACDA 3 ACDF 3 ACD 2
	Straight	9	
	No FU	1	
Straight	Straight	25	Straight to lordosis ACDA1 ACDF 3 ACD 4
	Lordosis	8	
	Kyphosis	1 (straight after 5 yrs)	
	No FU	7	
Kyphosis	Kyphosis	1	Straight to lordosis ACD 1
	Straight	5	
	Lordosis	1	

Table 5

	ACDA	ACDF	ACD	Total
5-year follow-up	Average annual reoperation rate (%) for adjacent level disease			
Goedmakers (current study)	1.9	1.8	0	1.2
MacDowall (MacDowall A, 2019)	1.8	1.4	n.a.	1.5
Burkus (Burkus JK, 2010)	1.1	2.0	n.a.	1.5
Delamarter (Delamarter RB, 2013)	0.6	2.9	n.a.	1.7
Donk (Donk RD, 2018)	0	1.2	0.8	0.7

Table 6

	ACDA	ACDF	ACD	Total
5-year follow-up	Average annual reoperation rate (%) at index level			
Goedmakers (current study)	0.6	0.6	2.5	1.2

MacDowall (MacDowall A, 2019)	3.6	0.6	n.a.	2.0
Burkus (Burkus JK, 2010)	1.5	5.0	n.a.	3.2
Delamarter (Delamarter RB, 2013)	0.3	2.6	n.a.	1.4
Donk (Donk RD, 2018), 9 yr	0.2	0.2	0.3	0.2