Randomized Controlled Trial

The Effect of Percutaneous Nucleoplasty vs Anterior Discectomy in Patients with Cervical Radicular Pain due to a Single-Level Contained Soft-Disc Herniation: A Randomized Controlled Trial

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

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

Study Design: A randomized, controlled, multi-center trial.

Setting: Medical University Center and local hospitals.

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

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

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

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

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

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Cervical radicular pain (CRP) is a common problem in the adult population (1,2). Each year 83.2 patients in a population of 100.000 persons are affected (3). CRP usually presents with pain in the neck, then radiates into the arm and fingers (2,4). In the majority of patients, the natural course of CRP is favorable (2,3,5). However, when conservative treatment (CT), such as anti-inflammatory medications, immobilization, physiotherapy (PT), and epidural steroid injections (2,6,7), fails and the severe pain persists, surgical treatment is considered (7). The most common surgical technique for treating CRP due to a disc herniation, involves the removal of the herniated disc, typically followed by fusion of the 2 adjacent vertebral bodies (8,9). We prefer the ACD technique, which is an accepted surgical treatment for patients with CRP (10-12). But nowadays, the ACD with fusion technique (ACDF) is seen as the gold standard (12,13). The rationale of ACDF is to maintain cervical lordosis, to avoid kyphotic spine deformation, and to prevent motion of the cervical spine so that arthrodesis can occur in a more stable environment (14). However, solid proof for the superiority of ACDF is lacking and 2 recent randomized trials comparing ACD to ACDF with intervertebral cage or with disk prosthesis in patients with CRP, show similar results on neck and arm pain, disability due to neck pain, and quality of life (10,12).

Surgery is also associated with some rare, but serious complications, such as oesophageal injury, postoperative hematoma, mortality (8,15,16), and adjacent level disease (10,12,17). To further reduce these risks, new minimally invasive treatments for vertebral disc diseases have been developed in the last 3 decades. One such technique is percutaneous cervical nucleoplasty (PCN), it uses coblation technology for ablating and coagulating soft-tissue of the herniated disc (18). This causes disc decompression, reducing intradiscal pressure, and hence relieves the internal forces that cause irritation of the adjacent nerve root (18,19). It induces the down-regulation of local inflammatory mediators, reduces disc size, and initiates the healing process, all contributing to a reduction of radicular pain (20). Several studies have shown that PCN is a safe and effective technique with good results (i.e., 60 to 85 percent of patients have good to excellent patient satisfaction after a PCN) (1,21-25). The procedure can be performed under local anesthesia. This also reduces the risk of trauma and provides shorter convalescence (21,26) with no reported neurological complications of the procedure itself (27,28). The objective of this randomized controlled trial (RCT) is to compare the effects of PCN and ACD in a group of patients with CRP caused by a single-level contained soft-disc herniation.

Methods

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

Study Design

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

Patients

Eventually, patients were randomly assigned to one of 2 groups: PCN or ACD. Patients were included if they reported complaints of radicular pain of the lower cervical spine (C4 – C7) as a result of a single-level contained soft-disc hernia with or without neck pain and without improvement after at least 8 weeks of CT, such as anti-inflammatory medications, immobilization, PT, and epidural steroid injections. In addition, the intensity of their radicular arm pain had to be at least 50 millimetres (mm) on a visual analog scale (VAS) (0 = no pain and 100 = the worst pain imaginable). Excluded were patients with previous spinal surgery in the cervi-

cal region, an extruded disc fragment, a bony spur, a calcified disc, or severe degenerative disc disease with more than 50 percent loss of disc height. All patients were diagnosed by a neurologist based on clinical history, physical examination, and magnetic resonance imaging (MRI). They were also examined using needle electromyography to assess nerve root function and to rule out other neurological causes, such as ulnar or median entrapment neuropathies or peripheral neuropathy. Patients were recruited by the neurosurgeons of the Erasmus University Medical Center Rotterdam and the participating centers. Eligible patients were referred to an experienced staff neurosurgeon (B.H.) of the Erasmus University Medical Center Rotterdam or the St. Franciscus Gasthuis Rotterdam, who screened and included the patients. All patients gave written informed consent before enrollment into the trial. The results are reported in accordance with the updated guidelines of the Consolidated Standards of Reporting Trials (CONSORT) statement (27).

Interventions

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

Outcomes

The primary outcome measure was arm pain intensity measured with the VAS (31).The VAS was measured on a horizontal 100 mm scale varying from 0 mm (no pain) to 100 mm (most intensive pain). The VAS has an adequate reliability and excellent validity in patients with chronic pain (32,33).

Secondary outcome measures were arm pain intensity during heavy effort measured with the VAS (such as squeezing, wringing, or typing) (31), neck pain intensity measured with the VAS (31), and satisfaction and improvement after the treatment measured with the global perceived effect questionnaire (GPE) (34). GPE measures patient satisfaction and improvement after a treatment using a 7-point Likert scale (34,35). Patient satisfaction was measured by answering the question: How satisfied are you with your treatment: 1 = very much satisfied to 7 = not at all satisfied. Improvement was measured by answering the question: Since the start of treatment, my current overall status is: 1 = very much improved to 7 = very much worse (35). The GPE is regarded as valid and reliable (36).

In addition, disability due to neck pain was measured using the Neck Disability Index (NDI) (37). The NDI is the most often used outcome measure for self-reported disability in patients with neck pain (37).The NDI is a 10-item questionnaire that measures pain intensity, daily work-related activities, and nonwork related activities (38). The maximum score is 50. Scores of < 4 indicate no disability, 5 to 14 indicate mild disability, 15 to 24 moderate disability, 25 to 34 severe disability, and scores above 35 indicate complete perceived disability. This 50-point score was converted to a 100-point scale, where lower scores indicate less disability (38). The NDI is reliable and valid for patients with cervical pathology (36,37,39).

Generic health status was measured as well, using the Short Form Generated Health Survey (SF-36) (40). The SF-36 consists of 36 items on physical and social status of the patient divided into 8 subscales: 1-physical functioning, 2-role limitation due to physical health problems, 3-bodily pain, 4-general health perceptions, 5-vitality, 6-social functioning, 7-role limitations due to emotional problems, and 8-general mental health. The items were scored on a scale of 0 = worst health to 100 = ideal health. A higher score means a better self-reported health (40). The SF-36 has a good reliability and validity (33).

We also recorded the number, nature, and severity of complications of the interventions.

All parameters were measured at baseline (T0), 3 months after intervention (T2), and one year after intervention (T3). One week after the intervention (T1) an intermediate assessment of arm pain, arm pain during heavy effort, and neck pain, was performed using the VAS and satisfaction and improvement were measured with the GPE. The assessments were performed at the Research Unit of the Center for Pain Medicine of the Erasmus University Medical Center Rotterdam.

Sample Size

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

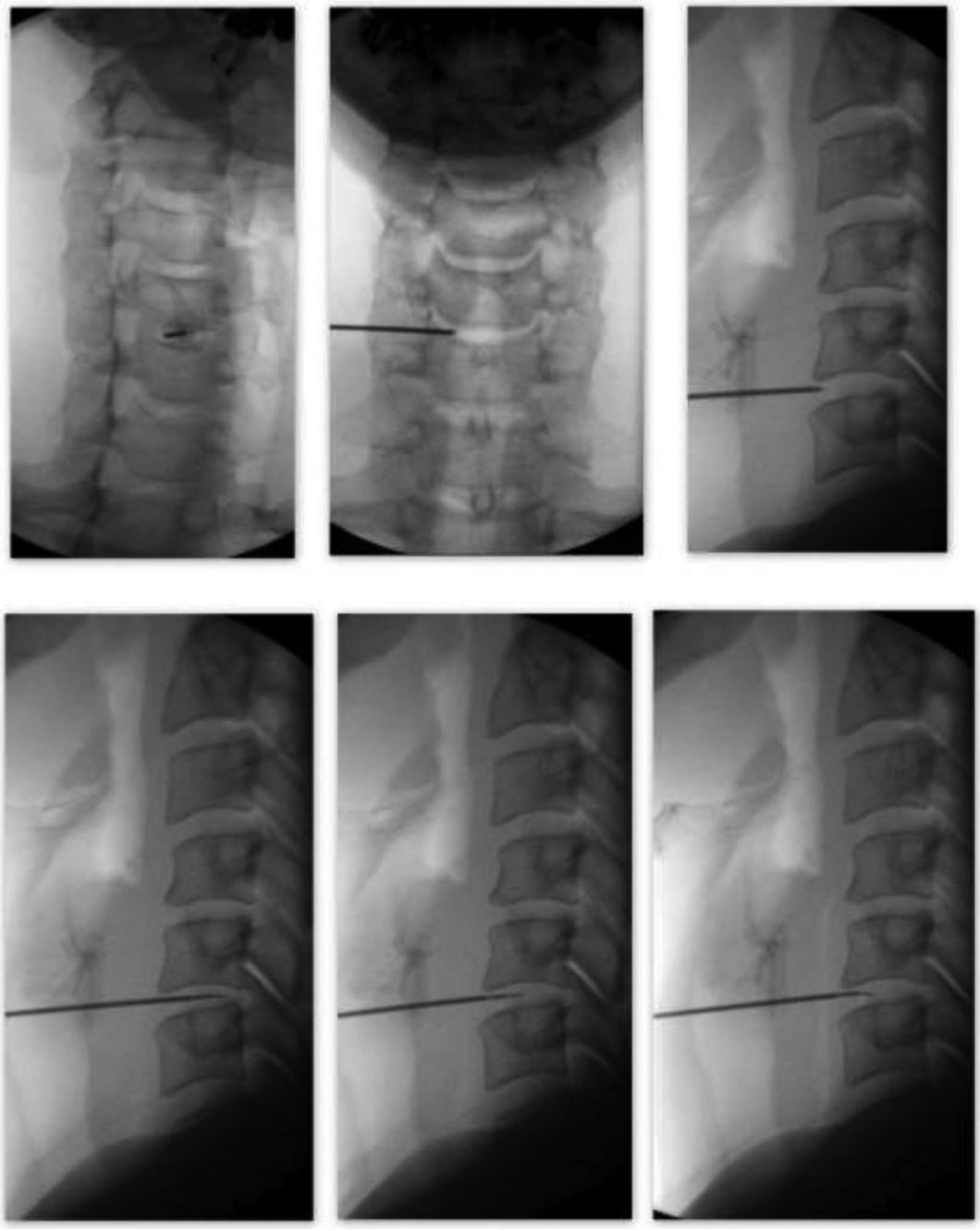

Fig. 1. *Technique of percutaneous cervical nucleoplasty.*

Randomization

After providing written informed consent, the patients were randomized according to a computer-generated non-stratified block randomization program (www. randomization.com). An independent observer, who was not involved in the patients' outcome assessments, provided the trial coordinator with sealed envelopes containing the randomization assignments. Envelopes were labelled according to the identification number of the study patients. For eligible patients,

envelopes were opened in ascending order by the trial coordinator to determine the group allocation.

Blinding

Due to the nature of the interventions, it was not possible to blind the interventionists and the patients. The data were analysed blindly.

Statistical Methods

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

Results

Sixty-seven eligible patients were screened for participation in this trial. Nineteen of them declined to participate, of whom 9 patients preferred a minimally invasive treatment with PCN and 8 patients preferred surgery. Two patients had less complaints and a wait and see policy was advised. Finally, 48 patients met the inclusion criteria and participated in this RCT. In Fig. 2, the flowchart according to the Consolidated Standards of Reporting Trials is reported.

The intended number of 94 patients was not achieved due to a low inclusion rate. It was estimated that the study would be finished after 2.5 years, but after one year we only enrolled 8 patients. After the adjustment of our protocol, we also expanded the trial with 3 centers to improve the inclusion rate. Despite this expansion the inclusion rate remained low and we decided to stop the trial. The last evaluation of the last included patient ended on March 2018. Forty-eight patients were randomly allocated to PCN (n = 24) and ACD (n = 24). No significant differences in baseline characteristics of the patients between the treatment groups were found (Table 1). The results of the descriptive statistics of the primary and secondary outcomes over time for both groups are presented in Table 2.

Outcomes

ITT Analyses: Baseline Compared to 3 Months

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

ITT Analyses: Baseline Compared to 12 Months

Regardless of the intervention made, all pooled patients improved significantly over time on the primary outcome arm pain and on the secondary outcomes arm pain during heavy effort, neck pain, NDI and the SF-36 items physical functioning, physical role limitations, mental health, vitality and pain. We did not find a statistically significant group effect on the primary and secondary outcomes and no statistically significant interactions on the primary and secondary outcomes (Table 3).

PP Analyses: Differences with Respect to the ITT-Analysis

At 3 months, the results of the PP analyses was almost the same as the ITT analyses. An additional statistically significant effect was found on the time factor of the secondary outcome satisfaction of the GPE (F(1,40) = 4.818; P = 0.03) (Table 3). At 12 months, the results of the PP analyses was also almost the same as the ITT analyses, but an additional statistically significant interaction was found on the item of general health of the

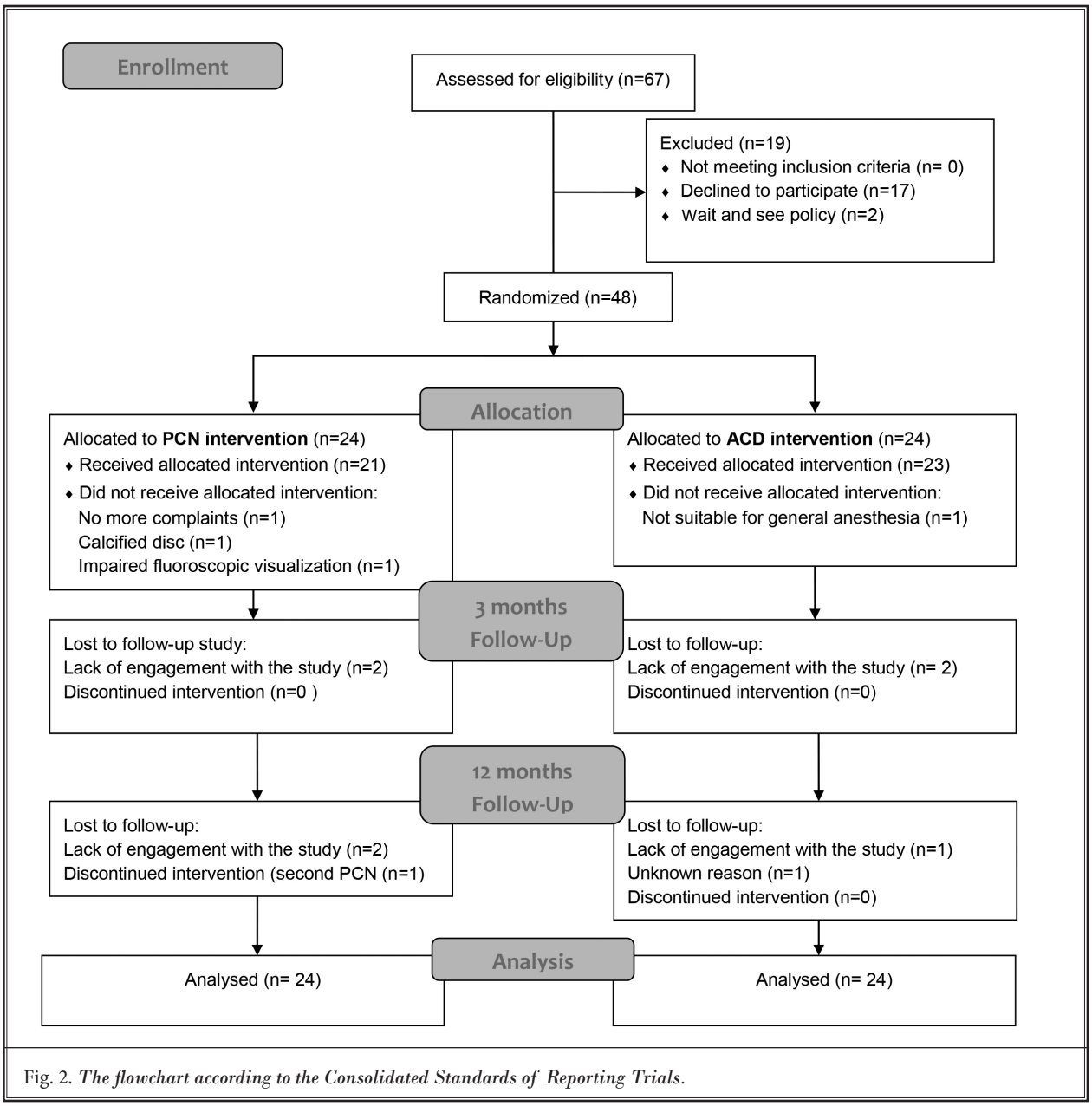

Fig. 2. *The flowchart according to the Consolidated Standards of Reporting Trials.*

SF-36 (F(1,39) = 4.290; *P* = 0.05), which was in favor of the ACD group (Table 3).

Adverse Effects

Three patients in the ACD group experienced adverse effects that were directly related to the operation. Two of these patients had severe postoperative neck pain and were treated with a stiff neck collar. In both patients, the neck pain disappeared within 3 months. Another patient in the ACD treatment group experienced postoperative dysphonia and dysphagia, which fully resolved within 3 months. In one patient who was treated with ACD, the complaints continued after surgery. However, this event was not directly related to the operation, a new MRI was performed and showed that the disc herniation was treated successfully. In the PCN group, no adverse events occurred directly related to the procedure. Two patients could not be treated with PCN due to the fact that the pain-specialist was not able to insert the introducer cannula into the herniated disc; we have described these failed

procedures earlier in the results. Eventually, both of these patients were sent to the neurosurgeon and were successfully treated with an ACD. Another patient in the PCN group developed a cervical disc herniation on the adjacent lower level (C4-5) 3 months after the intervention. A MRI was performed and showed new global bulgings of the discs C4-5 and C5-6. This patient was also successfully treated with an ACD at C5-6, but kept postoperative complaints of dysphagia. One patient in the PCN group, who was initially treated successfully, experienced CRP again 6 months after the treatment. A MRI showed a bulging disc at the same level as before. This patient preferred to be treated with PCN again and this was done successfully.

Discussion

In this trial, the effects of PCN were compared to ACD in 48 patients with CRP caused by a single-level contained soft-disc hernia. Three months after the intervention the ACD patients reported statistically significant less arm pain than the PCN patients. At 12 months, only a trend was found for more improvement on arm pain in the ACD group. Furthermore, no statisti-

Table 1. *Patient characteristics at baseline according to study arm.*

Item	PCN group	ACD group	*P* value
Age (SD)	47 (9.24)	50 (9.24)	0.122 †
Gender n (%)			0.085 ≠
Male	10 (41.7)	12 (45.8)	
Female	14 (58.3)	13 (54.2)	
Level of CHNP n (%)			2.087 ≠
C4-5		1 (4.2)	
C5-6	13 (54.2)	9 (37.5)	
C6-7	11 (45.8)	14 (58.3)	
Treatment location n (%)			0.085 ≠
Right	10 (41.7)	11 (45.8)	
Left	14 (58.3)	13 (54.2)	
Total duration of pain in months mean (SD)	18.17 (23.9)	22.8 (30.9)	0.309 †

CHNP, cervical hernia nucleus pulposus; SD, standard deviation, †, t-test; ≠, pearson-χ^2.

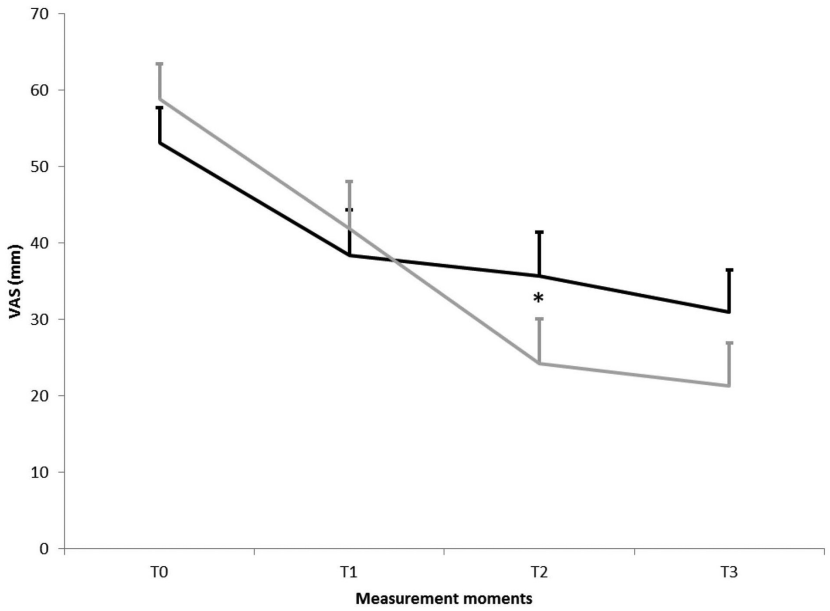

Fig. 3. *The intensity of arm pain between treatment groups at all measurement moments.*
*$P < 0.05$; PCN, percutaneous cervical nucleoplasty group depicted as black; ACD, anterior cervical discectomy group depicted as grey.

Table 2. *The results of the descriptive statistics of the primary and secondary outcomes over time for both groups.*

Outcomes	ITT analyses		PP analyses	
	PCN group	ACD group	PCN group	ACD group
VAS arm (mm)				
Baseline	53.1 (4.60) [43.8-62.4]	58.9 (4.61) [49.7-68.3]	53.2 (4.59) [43.9-62.4]	58.9 (4.61) [49.6-68.2]
1 week	38.4 (6.00) [26.3-50.5]	41.9 (6.13) [29.6-54.3]	38.6 (6.17) [26.1-51.0]	38.7 (6.43) [25.7-51.7]
3 months	35.7 (5.74) [24.1-47.2]	24.3 (5.75) [12.7-35.9]	34.1 (5.80) [22.5-45.8]	18.3 (4.61) [6.43-30.1]
12 months	31.0 (5.49) [19.9-42.1]	21.3 (5.61) [10.0-32.6]	34.2 (5.61) [22.9-45.6]	19.5 (0.62) [07.0-31.9]
VAS arm during activities (mm)				
Baseline	70.4 (4.14) [62.0-78.7]	72.4 (4.23) [63.8-80.9]	70.4 (4.14)[62.0-78.7]	72.4 (4.23) [63.8-80.8]
1 week	35.9 (6.07) [30.6-56.5]	48.1 (6.20) [35.6-60.6]	52.4 (6.30) [39.7-65.1]	45.4 (6.43) [32.5-58.4]
3 months	43.5 (6.43) [30.6-56.5]	40.7 (6.57) [27.5-53.9]	42.7(6.80) [28.9-56.3]	40.7 (6.83) [26.9-54.5]
12 months	43.6 (6.38) [30.7-56.4]	32.0 (6.51) [18.9-45.1]	44.9 (7.08) [30.6-59.2]	29.7 (7.09) [15.4-44.1]
VAS neck (mm)				
Baseline	60.1 (4.60) [50.8-69.4]	59.9 (4.92) [50.1-69.9]	60.1 (4.60) [50.8-69.4]	60.1 (4.93) [50.1-70.0]
1 week	46.7 (5.55) [35.5-57.9]	48.9 (6.16) [50.5-70.4]	45.2 (5.77) [33.5-56.8]	46.5 (6.51) [33.3-59.6]
3 months	37.1 (5.70) [26.3-49.3]	26.0 (5.96) [13.9-38.0]	35.6 (5.90) [23.7-47.5]	24.5 (5.95) [12.5-36.6]
12 months	35.0 (5.41) [24.1-45.9]	24.7 (5.53) [13.5-35.8]	35.3 (5.64) [23.9-46.7]	21.2 (5.65) [09.7-32.6]
GPE-Satisfaction*				
1 week	2.95 (0.29) [2.37-3.55]	2.46 (0.29) [1.83-3.06]	2.95 (0.29) [2.37-3.55]	2.46 (0.29) [1.83-3.06]
3 months	2.60 (0.34) [1.92-3.28]	1.97 (0.35) [1.26-2.67]	2.60 (0.34) [1.93-3.28]	1.97 (0.35) [1.26-2.67]
12 months	3.00 (0.32) [2.36-3.64]	2.27 (0.32) [1.62-2.92]	2.21 (0.31) [1.58-2.84]	1.80 (0.30) [1.19-2.41]
GPE-Improvement				
1 week	2.91 (0.25) [2.42-3.41]	2.90 (0.25) [2.40-3.41]	2.91 (0.25) [2.42-3.41]	2.90 (0.25) [2.40-3.41]
3 months	2.87 (0.29) [2.29-3.45]	2.34 (0.29) [1.75-2.93]	2.87 (0.29) [2.28-3.45]	2.34 (0.29)[1.75-2.93]
12 months	3.00 (0.32) [2.36-3.64]	2.27 (0.32) [1.62-2.92]	2.89 (0.35) [2.18-3.61]	2.26 (0.34) [1.57-2.96]
NDI*				
Baseline	61.88 (2.83) [56.17-67.59]	67.70 (2.83) [61.99-73.41]	61.88 (2.83) [56.17-67.59]	67.70 (2.83) [61.99-73.41]
3 months	49.09 (4.31) [40.40-57.76]	49.79 (4.31) [41.12-58.48]	48.68 (04.28) [40.03-57.32]	48.92 (4.28) [40.28-57.56]
12 months	46.13 (4.36) [37.35-54,91]	46.35 (4.36) [37.57-55.13]	46.01 (4.59) [36.71-55.30]	44.52 (4.59) [35.22-3.81]
SF-36**				
Physical functioning baseline	60.00 (3.70) [52.55-67.46]	55.44 (3.78) [47.82-63.05]	60.00 (3.70) [52.55-67.46]	55.44 (3.78) [47.82-63.05]
3 months	66.67 (4.70) [57.19-76.14]	66.96 (4.80) [57.28-76.63]	67.46 (4.73) [57.93-77.00]	67.46 (4.73) [57.93-77.00]
12 months	72.50 (5.05) [62.33-82.68]	70.65 (5.16) [60.26-81.05]	73.25 (5.37) [62.40-84.09]	73.09 (5.39) [62.20-83.98]
Social functioning baseline	58.85 (5.04) [48.69-69.01]	53.80 (5.04) [48.69-69.01]	58.85 (5.04) [48.69-69.01]	53.80 (5.04) [48.69-69.01]
3 months	66.67 (5.41) [55.77-77.56]	66.30 (5.53) [55.18-77.43]	67.64 (5.49) [56.58-78.71]	67.30 (5.53) [56.14-78.47]
12 months	68.75 (5.97) [56.74-80.76]	72.28 (6.09) [60.01-84.56]	69.08 (6.43) [56.11-82.06]	75.52 (6.45) [62.49-88.55]
Physical role limitations baseline	21.88 (4.68) [12.45-31.30]	8.69 (4.78) [-0.93-18.32]	21.88 (4.68) [12.45-31.30]	8.69 (4.78) [-0.93-18.32]
3 months	35.42 (8.78) [17.73-53.11]	34.78 (8.97) [16.71-52.85]	37.26 (9.20) [18.71-55.82]	36.09 (9.22) [17.48-54.70]
12 months	59.38 (9.42) [40.39-78.36]	52.17 (9.63) [32.79-71.56]	64.46 (9.76) [44.42-83.89]	59.38 (9.77) [39.62-79.14]
Emotional role limitations baseline	63.89 (8.83) [46.11-81.67]	73.91(9.02) [55.75-92.08]	63.89 (8.83) [46.11-81.67]	73.91 (9.02) [55.75-92.08]
3 months	73.61 (9.12) [55.24-91.99]	65.21 (9.32) [46.45-83.99]	77.04 (9.10) [58.68-95.39]	65.63 (9.16) [47.14-84.12]
12 months	75.00 (8.71) [57.45-92.55]	72.46 (8.90) [54.54-90.39]	64.16 (9.75) [44.42-83.89]	59.38 (9.77) [39.62-79.14]

Table 2 cont. *The results of the descriptive statistics of the primary and secondary outcomes over time for both groups.*

Outcomes	ITT analyses		PP analyses	
	PCN group	ACD group	PCN group	ACD group
Mental health baseline	68.00 (3.63) [60.68-75.32]	69.04 (3.71) [61.56-76.52]	68.00 (3.63) [60.68-75.32]	69.04 (3.71) [61.56-76.52]
3 months	72.83 (3.32) [66.16-79.51]	72.00 (3.39)[65.18-78.82]	73.58 (3.26) [67.01-80.15]	72.28 (3.31) [65.61-78.95]
12 months	73.33 (3.13) [67.03-79.64]	73.04 (3.19) [66.60-79.49]	73.52 (3.07) [67.32-79.72]	74.13 (3.11) [67.84-80.43]
Vitality baseline	46.46 (3.70) [38.99-53.92]	42.61 (3.78) [34.99-50.23]	46.46 (3.70) [38.99-53.92]	42.61 (3.78) [34.99-50.23]
3 months	60.42 (4.78) [50.79-70.05]	51.96 (4.88) [42.12-61.79]	61.83 (4.72) [52.32-71.34]	52.42 (4.78) [42.79-62.05]
12 months	62.71 (4.57) [53.52-71.90]	55.44 (4.66) [46.05-64.82]	64.15 (4.73) [54.61-73.69]	55.56 (4.76) [45.94-65.18]
Pain baseline	38.18 (3.78) [30.57-45.79]	29.02 (3.86) [21.25-36.79]	38.18 (3.78) [30.57-45.79]	29.02 (3.86) [21.25-36.79]
3 months	52.64 (5.35) [41.86-63.42]	59.63 (5.47) [48.61-70.64]	54.29 (5.45) [43.30-65.28]	61.14 (5.47) [50.10-72.17]
12 months	63.61 (5.48) [52.58-74.63]	62.38 (5.59) [51.11-73.64]	65.22 (5.92) [53.23-77.19]	64.19 (5.92) [52.21-76.18]
General Health baseline	62.71 (4.29) [54.06-71.36]	55.65 (4.39) [46.82-64.49]	62.71 (4.29) [54.06-71.36]	55.65 (4.39) [46.82-64.49]
3 months	68.96 (4.51) [59.88-78.03]	55.22 (4.60) [45.95-64.49]	70.15 (4.52) [61.04-79.27]	55.41 (4.57) [46.21-64.62]
12 months	63.33 (4.65) [53.97-72.70]	65.21 (4.7 5) [55.65-74.79]	61.42 (4.91) [51.49-71.35]	66.66 (4.95) [56.65-76.68]

Data are presented as Mean (Standard Error) [95% Confidence Interval] of the linear mixed-model analyses. *A lower score means better outcomes with regard to satisfaction and improvement (GPE) and less disability in daily activities due to neck pain (NDI). **A higher score means a better health-related quality of life status (SF-36).

cally significant interactions were found on the secondary outcomes.

There are only a few studies comparing PCN to surgery. The first study is a recently performed RCT that compared the effects of PCN to posterior decompression in patients suffering from single level disc herniation with an indication for surgery (n = 35) (41). In this trial, no significant differences were found between the groups on radicular arm pain and neck pain 3 and 6 months after the intervention (41). A second study was a retrospective study that compared PCN (n = 81) to ACD (n = 95) in patients with a contained disc herniation (25). At about 29 months, they did not find a statistically significant difference in pain reduction between PCN and ACD. The findings of the first study (41) is in contrast with the findings of our study at 3 months. However, at the longer-term (i.e., 6 months and longer), the results of these studies (25,41) might be in confirmation with our trial results.

The success rate of PCN depends on strict patient selection (21). Two recent retrospective studies examined the ideal selection criteria of a successful PCN (21,42) and found that the following selection criteria are predictive for a positive outcome of PCN: MRI confirmed one-level contained herniated discs, minimally degenerated discs, short mean pain duration of respectively 6, 8 (42), and 16 months (21), absence of central canal stenosis, and unilateral radicular pain rather than bilateral radicular or axial neck pain only (21,42). The inclusion criteria of our patients matched with these criteria with the exception of a short pain duration. The mean pain duration of our PCN group was at baseline 18.17 months, which fell within the range of the mean pain duration of patients with a negative outcome of the PCN procedure, respectively 10.85 (42) to 37 months (21). This may have had a negative impact on the outcomes of our PCN group.

At 3 months, our ACD patients showed statistically significant more reduction in arm pain intensity compared to the PCN patients, namely an average of 17.2 mm on a VAS scale of 100 mm. It is debatable whether or not this difference is of clinical relevance. To further investigate clinical relevance of this difference, we divided the patients into those who showed an improvement in arm pain of ≥ 30.0 mm on the VAS and those who did not. A mean reduction in VAS of 30 mm represents a clinically important difference in pain severity that corresponds to patients' perception of adequate pain control (43). We found that the proportion of patients who met this criterion did not differ between the experimental groups ($P = 0.11$, Fisher's Exact Test 2-sided). Considering this, the absence of a difference in arm pain relief between the groups after one year, the smaller number of complications within the PCN group, and the minimally invasive technique of PCN, we argue that PCN can be a good alternative to ACD, certainly from a longer-term perspective.

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

ITT analyses				
Outcomes	**Between Groups**	**Time**	**Interaction between group and time**	**Group**
	P Value	**P Value**	**P Value**	**P Value**
Visual Analog Scale Arm pain				
3 months	$F_{(1,45)} = 0.204$; $P = 0.65$	$F_{(1,44)} = 38.154$; $P < 0.001$***	$F_{(1,44)} = 4.131$; $P = 0.05$*	$F_{(1,45)} = 0.615$; $P = 0.44$
12 months	$F_{(1,45)} = 0.920$; $P = 0.76$	$F_{(1,45)} = 41.246$; $P < 0.001$***	$F_{(1,45)} = 3.052$; $P = 0.09$	$F_{(1,44)} = 0.156$; $P = 0.69$
Arm pain during activities				
3 months	$F_{(1,45)} = 0.005$; $P = 0.95$	$F_{(1,45)} = 047.797$; $P < 0.001$***	$F_{(1,45)} = 0.324$; $P = 0.57$	$F_{(1,44)} = 0.000$; $P = 0.99$
12 months	$F_{(1,45)} = 0.623$; $P = 0.43$	$F_{(1,45)} = 51.136$; $P < 0.001$***	$F_{(1,45)} = 2.085$; $P = 0.16$	$F_{(1,40)} = 1.048$; $P = 0.31$
Neck pain				
3 months	$F_{(1,41)} = 0.858$; $P = 0.36$	$F_{(1,40)} = 51.402$; $P < 0.001$***	$F_{(1,40)} = 2.207$; $P = 0.15$	$F_{(1,41)} = 0.754$; $P = 0.39$
12 months	$F_{(1,44)} = 0.685$; $P = 0.41$	$F_{(1,44)} = 43.347$; $P < 0.001$***	$F_{(1,44)} = 1.536$; $P = 0.22$	$F_{(1,42)} = 1.414$; $P = 0.24$
Global perceived effect Satisfaction				
3 months	$F_{(1,43)} = 1.881$; $P = 0.18$	$F_{(1,43)} = 4.967$; $P = 0.31$	$F_{(1,43)} = 0.088$; $P = 0.77$	$F_{(1,43)} = 1.931$; $P = 0.17$
12 months	$F_{(1,42)} = 2.038$; $P = 0.16$	$F_{(1,42)} = 6.997$; $P = 0.18$	$F_{(1,42)} = 0.029$; $P = 0.87$	$F_{(1,42)} = 2.038$; $P = 0.16$
Improvement				
3 months	$F_{(1,44)} = 0.630$; $P = 0.43$	$F_{(1,44)} = 1.756$; $P = 0.19$	$F_{(1,44)} = 1.249$; $P = 0.27$	$F_{(1,44)} = 0.744$; $P = 0.39$
12 months	$F_{(1,36)} = 1.269$; $P = 0.27$	$F_{(1,36)} = 1.269$; $P = 0.28$	$F_{(1,36)} = 1.143$; $P = 0.29$	$F_{(1,36)} = 1.056$; $P = 0.31$
Neck Disability Index				
3 months	$F_{(1,44)} = 0.506$; $P = 0.48$	$F_{(1,44)} = 43.006$; $P < 0.001$***	$F_{(1,44)} = 1.191$; $P = 0.28$	$F_{(1,44)} = 0.478$; $P = 0.44$
12 months	$F_{(1,44)} = 0.494$; $P = 0.49$	$F_{(1,44)} = 40.154$; $P < 0.001$***	$F_{(1,44)} = 0.916$; $P = 0.34$	$F_{(1,40)} = 0.247$; $P = 0.62$
Short Form-36 − Physical functioning				
3 months	$F_{(1,45)} = 0.148$; $P = 0.70$	$F_{(1,45)} = 14.748$; $P < 0.001$***	$F_{(1,45)} = 1.051$; $P = 0.31$	$F_{(1,45)} = 0.159$; $P = 0.69$
12 months	$F_{(1,45)} = 0.340$; $P = 0.56$	$F_{(1,45)} = 19.452$; $P < 0.001$***	$F_{(1,45)} = 0.187$; $P = 0.67$	$F_{(1,43)} = 0.185$; $P = 0.67$
Social functioning				
3 months	$F_{(1,45)} = 0.159$; $P = 0.69$	$F_{(1,45)} = 10.603$; $P < 0.002$**	$F_{(1,45)} = 0.565$; $P = 0.46$	$F_{(1,43)} = 0.159$; $P = 0.69$
12 months	$F_{(1,45)} = 0.045$; $P = 0.83$	$F_{(1,45)} = 0.158$; $P = 0.22$	$F_{(1,45)} = 0.369$; $P = 0.55$	$F_{(1,46)} = 0.010$; $P = 0.92$
Physical role limitations				
3 months	$F_{(1,45)} = 0.710$; $P = 0.40$	$F_{(1,45)} = 11.556$; $P < 0.001$***	$F_{(1,45)} = 1.158$; $P = 0.29$	$F_{(1,44)} = 0.745$; $P = 0.39$
12 months	$F_{(1,45)} = 1.463$; $P = 0.23$	$F_{(1,45)} = 38.931$; $P < 0.001$***	$F_{(1,45)} = 0.212$; $P = 0.65$	$F_{(1,43)} = 1.160$; $P = 0.29$
Emotional role limitations				
3 months	$F_{(1,45)} = 0.005$; $P = 0.94$	$F_{(1,45)} = 0.08$; $P = 0.93$	$F_{(1,45)} = 2.628$; $P = 0.11$	$F_{(1,44)} = 0.004$; $P = 0.95$
12 months	$F_{(1,45)} = 0.132$; $P = 0.72$	$F_{(1,45)} = 0.461$; $P = 0.50$	$F_{(1,45)} = 0.779$; $P = 0.38$	$F_{(1,42)} = 0.392$; $P = 0.53$
Mental health				
3 months	$F_{(1,45)} = 0.000$; $P = 0.98$	$F_{(1,45)} = 8.776$; $P = 0.005$**	$F_{(1,45)} = 0.509$; $P = 0.48$	$F_{(1,45)} = 0.001$; $P = 0.98$
12 months	$F_{(1,45)} = 0.007$; $P = 0.94$	$F_{(1,45)} = 10.451$; $P = 0.002$**	$F_{(1,45)} = 0.213$; $P = 0.65$	$F_{(1,44)} = 0.033$; $P = 0.86$
Vitality				
3 months	$F_{(1,45)} = 1.166$; $P = 0.29$	$F_{(1,45)} = 27.833$; $P < 0.001$***	$F_{(1,45)} = 1.089$; $P = 0.30$	$F_{(1,45)} = 1.405$; $P = 0.24$
12 months	$F_{(1,45)} = 1.057$; $P = 0.31$	$F_{(1,45)} = 35.034$; $P < 0.001$***	$F_{(1,45)} = 0.486$; $P = 0.49$	$F_{(1,44)} = 1.340$; $P = 0.25$
Pain				
3 months	$F_{(1,45)} = 0.038$; $P = 0.85$	$F_{(1,45)} = 40.809$; $P < 0.001$***	$F_{(1,45)} = 5.245$; $P = 0.03$*	$F_{(1,45)} = 0.043$; $P = 0.84$
12 months	$F_{(1,45)} = 1.003$; $P = 0.32$	$F_{(1,45)} = 47.222$; $P < 0.001$***	$F_{(1,45)} = 0.861$; $P = 0.36$	$F_{(1,43)} = 0.946$; $P = 0.34$
General Health				
3 months	$F_{(1,45)} = 3.205$; $P = 0.08$	$F_{(1,45)} = 1.446$; $P = 0.24$	$F_{(1,45)} = 1.911$; $P = 0.17$	$F_{(1,45)} = 3.612$; $P = 0.64$
12 months	$F_{(1,45)} = 0.203$; $P = 0.66$	$F_{(1,45)} = 3.265$; $P = 0.08$	$F_{(1,45)} = 2.513$; $P = 0.12$	$F_{(1,44)} = 0.024$; $P = 0.88$

Limitations

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

Conclusions

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

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Author Contributions

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

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