

Clinical management for cervical radiculopathy: A systematic review and meta-analysis

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Abstract

An inflamed or damaged nerve root in cervical spine is defined as cervical radiculopathy. The purpose of the current study is to recognize the most effective surgical procedures in cervical radiculopathy subjects. All related studies were taken using PubMed searching international databases, Scopus, ISI Web of Science (WoS), and Science direct with no limit of until November 20th, 2021. Finally, based on inclusion and exclusion criteria; after reviewing all randomized controlled trial studies those had the related data the researchers were looking for, conducted a meta-analysis with seven remaining studies including eight different treatments. Heterogeneity was evaluated by Cochran's Q and Higgins I² using R software for the network. In the results presented in this study, the neck disability index (NDI) changes as a result of taking cervical anterior discectomy without (ACD) and with fusion (ACDF) and ACD arthroplasty were -0.003, -1.659, and -1.656, respectively. According to final diagram of the network, 11 comparisons were made in pairs. When each treatment group is compared with ACDF, it is shown that there was a significant mean effect among the patients who receive Mobi-C, KineflxC, and ADR, with mean differences of -8.60 [CI 95% (-12.75, -4.45)], -1.10 [CI 95% (-5.22, 3.02)], and -1.00 [CI 95% (-7.18, 5.18)], respectively. The most effective surgical treatments for cervical radiculopathy were Mobi-c, KineflxC, and artificial disc replacement compared to ACDF treatment, respectively.

Keywords: Cervical radiculopathy, meta-analysis, network meta-analysis, surgical procedures

Introduction

An arm pain related to the involved cervical nerve root dermatome is called cervical radiculopathy (CR).^[1] Criteria are too different for choosing people who suffer from CR, but it is reported that the characteristics of the disease are neck pain and a sense of numbness in the neck and arm; neck movement is restricted and is associated with depression and insomnia. This disease significantly affects the patients' life quality.^[2-4] Because of a compressed nerve, patients with CR suffer from pain, abnormal sensation, weakness in muscles, reduced tendon reflexes, or muscle atrophy in the upper limb.^[2] Although the prevalence of CR is unclear and epidemiologic data are sparse, a study reported that the average incidence rate of CR per year is 83 per 100,000 for the entire population, whereas the prevalence increased, occurring in the fifth decade of life.^[1, 5]

At present, treatment for CR includes surgical and non-surgical approaches.^[6] Surgery is a valid and effective option when the pain is severe or not responding to conservative treatments.^[7] In a country like the Netherlands, with a population of about 17 million, an average of 2,000 patients undergo reception each year, resulting in a direct cost of around € 30 million a year.^[8] Among surgical options, the anterior approach is the most often used one, and cervical anterior discectomy without (ACD) and with fusion (ACDF) was developed during the 1950s and 1960s.^[9] Arthroplasty (artificial disc replacement) designed to maintain normal movement has been used because of the concern that the fusion may cause diseases in a nearby area.^[10] Recently, artificial disc replacement (ADR) has become another approach to fusion surgery.^[11] The Mobi-C prosthesis is a semi-restricted prosthesis consisting of a movable polyethylene core and two cobalt chrome plates.^[12] It has been reported that cervical disc arthroplasty (CDA)

with Mobi-C continues to be an effective and safe treatment method for the patients with one- or two-level cervical disc diseases.^[13]

The mainstay of treatment for CR is non-surgical management, and much of conservative treatment is concentrated on therapy and targeted cervical injections. However, for this approach, there are no ingrained non-surgical treatment guidelines based on the finest scientific evidence (CR and myelopathy). Conservative treatment includes drug treatment, physical therapy, and rehabilitation training. Among them, the drugs mainly involve anti-inflammatory analgesia, nerve edema, and neurotropic treatment, but there is no recognized prime drug.^[14]

A systematic review uses a method to identify all the studies for a specific focused purpose, evaluate methods, summarize study results, and identify reasons for different results in studies.^[15] Most systematic reviews focus on summarizing the benefits of one or more therapeutic interventions and side effects for a particular disease and helping to develop clinical knowledge in the future.^[16] This approach provides information about the benefits of interventions and their side effects and helps to improve clinical knowledge for further investigation.^[17] The difference between meta-analysis and systematic review is that instead of simple data collection and analysis, it uses statistical methods to quantitatively combine the results of multiple studies.^[18] Conventional meta-analyses are limited to direct comparisons and cannot provide information on the relative superiority of therapies that have not been directly compared,^[19] but network meta-analyses can overcome this limitation by including indirect comparisons as well as improving accuracy by combining direct and indirect estimation.^[20]

Three important hypotheses in network meta-analysis are as follows: Similarity: it requires the tests included to have significantly similar clinical and methodological characteristics (such as population and results) in comparison to some different sets of treatments (such as having different designs); homogeneity: this requires estimating the experiments' effects compared to similar treatments be homogeneous; consistency: this requires that estimations of the effect be consistent with different bases of evidence (such as direct and indirect comparisons).^[21] patients, and its prevalence is increasing. The aim of the current study is to recognize the best surgical treatments for CR disease. According to the searches, no systematic review and network meta-analyses have been performed to compare surgical treatments for CR so far. For this reason, we have collected and analyzed data from several research studies using a systematic review and network meta-analyses, which are often conducted in randomized controlled trials, and the results will be more reliable. This study provides new insights into surgical treatments of CR and shares good information for clinicians to manage and treat CR.

Materials and methods

The present study was carried out in conformity with the criteria of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA). Based on these criteria, systematic search in databases, documents' organization for review, criteria-centered selection of studies defined by the authors, the analysis of information extraction, and finally the presentation of the final report was performed.^[22]

Inclusion and exclusion criteria

Inclusion criteria can be mentioned as follows: a. RCT1 studies, b. studies conducted in English, and c. studies that assess the effect of surgical treatments on CR. Exclusion criteria: a. Observational studies (case-control and cohort), b. case reports, letter to editor, c. animal studies, d. studies where the full text is not available, e. unrelated studies, f. duplicate studies, and h. systematic review and meta-analysis studies.

Search strategy

In the systematic search, related articles were identified in four databases without time limit until 2021: PubMed, Scopus, Web of Science (WoS), and Science Direct. To find the appropriate keywords, the preliminary studies were published and medical subject headings (MESH terms) in the PubMed database as well as the questions of this study were carefully examined, and the keywords were chosen based on PICO criteria [participants: patients with CR; intervention surgical treatment for CR; comparison: the effects of the declared treatments on a decreased neck disability index (NDI) in participants; outcomes: recognizing the most effective treatment in decreased NDI]. Table (1) shows the keywords and search pattern in each of the databases. Selected keywords including cervical radiculopathy, surgical treatment, intervention, and synonyms were merged with the Boolean search method.

Table 1: Search strategies and keywords

PubMed	(cervical Radiculopathy [tiab]) AND (treatment[tiab] OR surgical treatment [tiab] OR surgery[tiab] OR medicine[tiab] OR manual opening therapy[tiab] OR manual traction [tiab] OR manual therapy [tiab] OR discectomy[tiab] OR foraminotomy[tiab] OR physiotherapy[tiab] OR exercise therapy[tiab] OR rehabilitation[tiab] OR arthroplasty[tiab] OR surgical intervention[tiab] OR conventional therapy [tiab]) AND (RCT [tiab] OR randomized control trial[tiab])	109
Scopus	TITLE-ABS (cervical Radiculopathy) AND TITLE-ABS (treatment OR surgical treatment OR surgery OR medicine OR manual opening therapy OR manual traction OR manual therapy OR discectomy OR foraminotomy OR physiotherapy OR exercise therapy OR rehabilitation OR arthroplasty OR surgical intervention OR conventional therapy) AND TITLE-ABS (rct OR Randomized Controlled Trial OR trial)	160
ISI WoS	TS (cervical Radiculopathy) AND TS (treatment OR surgical treatment OR surgery OR medicine OR manual opening therapy OR manual traction OR manual therapy OR discectomy OR foraminotomy OR physiotherapy OR exercise therapy OR rehabilitation OR arthroplasty OR surgical intervention OR conventional therapy) AND TS (rct OR Randomized Controlled Trial OR trial)	235
Science direct	Title, abstract, keywords: (cervical Radiculopathy) AND (treatment OR surgical treatment OR surgery OR manual traction OR manual therapy OR discectomy OR physiotherapy) AND (trial)	35

Information extraction and quality evaluation

After data extraction, the treatments were classified into 11 classes including ACD, ACDF, anterior cervical discectomy arthroplasty (ACDA), arthroplasty, fusion, KineflxC, minimally invasive posterior cervical foraminotomy (MI-PCF), CDA, two-level cervical total disc replacement (Mobi-C), artificial disc replacement (ADR), and anterior decompression combined with fusion.

Many indexes were reported for the assessment of CR in studies, but NDI was selected because of the high frequency of reports. NDI is a self-report questionnaire used to examine the self-rated disability among patients with neck pain and determine the effects of neck pain on a patient's daily life.^[23] In an Excel file, the mean and standard

deviation of NDI before and after treatment were extracted for all the groups to compute the effective size as the mean difference (MD). If the mean and standard deviation after treatment were not reported, they were estimated using mean NDI and standard deviation before treatment, respectively.

Statistical analysis

The differences of the groups were estimated by MD effect size. In each study, data related to the participants who accomplished post-treatment evaluations were used. Statistical software package R 4.1.2 was used for network meta-analysis calculations, and the Net-meta package was used to perform frequency-oriented network meta-analysis.

A fixed- or random-effects model was used to pool the data, where appropriate. Cochran’s Q test and I2 statistic were used to assess statistical homogeneity between the trials as a measure of variability. In this study analysis, Cochran’s test $P < 0.05$ and $I^2 > 50\%$ indicate relevant statistical heterogeneity.^[24] The Netgraph function of the Net-meta package in R software was used to estimate the geometry of the network. Also, in studies that have reported several follow-up periods, the shortest period is considered.

Results

As stated by the PRISMA guiding principle, studies which have been conducted in relation to surgical treatment for CR

were systematically reviewed. According to the primary search in the databases, 539 studies were gathered and moved to EndNote software. A total of 208 studies were repeated ones, 160 were unassociated, and 127 were eliminated by studying the title and abstract according to inclusion and exclusion criteria. After assessing the full text of the studies, all of them received acceptable methodological quality according to the CONSORT checklist score. After the quality assessment (QA), these seven studies went into the final stage analysis [Figure 1]. Table 2 shows the information regarding these seven studies.

Table 2: Information of studies included in the analysis step; mean age, sex, and treatment type

	1 st Author	Yr	Setting	Mean Age (Year±SD)			Total	Type	M/F	QA
				Treat1	Treat 2	Treat3				
1	Donk, R.D ^[9]	2017	USA	44.3±5.6	43.1±7.5	44.1±6.4	142	ACD ¹ ACDF ² ACDA ³	71/71	Exc
2	Coric, D ^[25]	2011	---	43.7±7.76	43.9±7.39	---	269	Kineflx/C ACDF	110/159	Exc
3	Dunn, C ^[26]	2018	USA	49.9±9.8	49±11.5	---	259	ACDF MI-PCF ⁴	133/126	Exc
4	Gornet, M.F ^[27]	2016	USA	44.5±8.8	43.9±8.8	---	545	CDA ⁵ ACDF	251/294	good
5	Radcliff, K ^[28]	2016	USA	45.3±8.1	46.2±7.9	---	330	Mobi-C ⁶ ACDF	158/172	Exc
6	keppholm, M ^[29]	2015	Swed	46.7±6.7	47±6.9	---	151	ADR7 ACDF	73/78	good
7	Vleggeert- Lankamp, C. L. A ^[30]	2019	Netherlands	46.4±7.3	47.5±8	46.5±8.7	109	ACD ACDF ACDA	51/58	Exc

Anterior Cervical Discectomy¹, Anterior Cervical Discectomy without Fusion², Anterior Cervical Discectomy Arthroplasty³, Minimally Invasive Posterior Cervical Foraminotomy⁴, Cervical Disc Arthroplasty⁵, 2-level cervical total disc replacement⁶, Artificial Disc Replacement⁷.

In the present study, NDI was used to compare surgical treatments. The cut-off value is essential to assess an individual patient or a certain group of patients for clinically important neck pain with disability by distinguishing it from insignificant pain.^[31] A column is defined for the cut-off point value of NDI in Table 3. The values of this cut-off point were different in the studies.

Based on the results shown in Table 3, NDI changed as a result of taking ACD and ACDF. The NDI changes of ACDA were -0.003, -1.659, and -1.656.^[9] In the study by Coric *et al.* ^[25] to evaluate the effect of KineflxC and ACDF, the NDI change was reduced by -31 and -28.5,

respectively. Dunn *et al.*'s.^[26] study of the effects of MI-PCF and ACDF showed an NDI change of -25.9 and -24.6, respectively. The study by Gornet *et al.* ^[27] also reported NDI changes of -54.638 and -55.599, respectively, in the effect of CDA and ACDF [Table 3]

Network meta-analysis results

First, the 13 studies were extracted. The effect size (TE) and the standard error (seTE) values were computed, and the related values were entered in the analysis step. Of these 13 studies, two studies involved three arms and the other studies involved two arms.

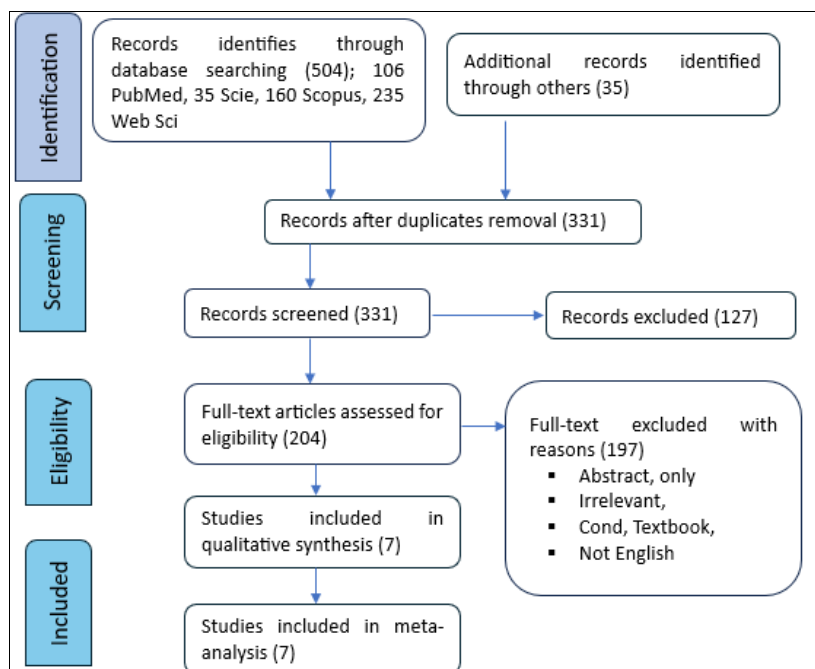


Fig 1: The flow chart indicating steps of systematic review and meta-analysis

Table 3: Information of studies included in analysis step; Initial mean NDI, mean NDI change, and final mean

S. No	1 st Author	Yr	Type	NDI	Cut-off point	Initial	Mean changes	Final	P-value
1	Donk, R.D [9]	2017	ACD ¹ ACDF ² ACDA ³	0-50	≤7	17.1/18.8/18.8	-0.003/-1.659/-1.656	17.097/17.141/17.144	0.249/0.237/0.998
2	Coric, D [25]	2011	KineflxC ACDF	0-100	≥40	63.2/61.8	-31/-28.5	32.2/33.3	0.05
3	Dunn, C [26]	2018	ACDF MI-PCF ⁴	--	--	35.6/34.2	-25.9/-24.6	9.7/9.6	0.8922
4	Gornet, M.F [27]	2016	CDA ⁵ ACDF	0-100	≥15	55.5/26.4	-54.638/-55.599	0.862/0.801	0.499
5	Radcliff, K [28]	2016	Mobi-C ⁶ ACDF	0-100	≥30	53.86/55.35	-28.16/-21.05	25.7/34.3	0.0029
6	keppholm, M [29]	2015	ADR ⁷ ACDF	0-100	--	64.6/61.4	-25.5/-21.3	39.1/40.1	0.77
7	Vleggeert-Lankamp, C. L. A [30]	2019	ACD ACDF ACDA	0-100	≤20	45/41/47	-24/-23/-29	21/18/18	0.711

Discussion

The goal of the present systematic review and network meta-analysis was to gather studies and combine those which are related to the effects of different surgical treatments for CR treatment and to specify the most effective treatments to reduce NDI in CR people. At the beginning, 13 studies were extracted, but six separate sub-networks were obtained. To obtain a single network, six studies were excluded, and an acceptable network was obtained with seven studies. Treatments including ACD, ACDA, KineflxC, MI-PCF, CDA, two-level cervical total disc replacement (Mobi-C), and ADR were compared with ACDF.

The results of the present study showed that Mobi-c surgical treatment was more effective than ACDF treatment in reducing the mean NDI of individuals. A study carried out by Ning Guang-Zhi *et al.* [32] in 2018 aimed to assess Mobi-C cervical disc arthroplasty (MCDA) versus fusion for the treatment of symptomatic cervical degenerative disc disease. In this meta-analysis article, four studies were combined to evaluate NDI scores between MCDA and ACDF, and 758 patients participated. The results in this study showed that MCDA was similar to ACDF in NDI and neck pain scores. Also, MCDA had lower neck pain scores, a greater motion range, and higher patient satisfaction scores than ACDF.[32] The difference between the results of the meta-analysis and the present study may be because of the sample size. As mentioned in this article, meta-analysis includes four studies, whereas the present study includes nine studies and the number of studies can affect the results. In another study by Radcliff *et al.*,[28] the results were similar to those of the present study. The aim of the study was to provide an evaluation of cervical total disc replacement (TDR) versus ACDF for the treatment of one- and two-level disc disease. Out of 330 participants, 225 patients were treated with Mobi-c and the rest were treated with ACDF in a 7-year follow-up period. The results showed that group Mobi-c had a significantly higher NDI success rate than group ACDF. Also, in a study conducted by Michael S. Hisey *et al.*,[33] the purpose was to compare the results of cervical total disc replacement (TDR) using the Mobi-C with ACDF. In this prospective, controlled trial, 245 randomized patients (2:1) received TDR with Mobi-C cervical disc prosthesis or ACDF with anterior plates and allograft. The result demonstrated that TDR with Mobi-C is a safety treatment compared to ACDF in the treatment of one-level symptomatic cervical degenerative disc disease. In the present study, KineflxC treatment was more effective than ACDF treatment in reducing NDI. In a study conducted by Domagoj Coric *et al.* [34] in 2018, the authors evaluated a

metal-on-metal TDR’s (KineflxC) efficacy and safety versus ACDF in the treatment of single-level spondylosis with radiculopathy. In this prospective multi-center study, 269 patients were chosen randomly to two groups including TDR (136 patients) using the KineflxC cervical artificial disc or ACDF (133 patients) using structural allograft and an anterior plate. Similar to the present study, the results of this study indicate that KineflxC TDR is a feasible alternative to ACDF. The objective of the study was to assess the preliminary clinical results for the simplify cervical artificial disc conducted by Maislin *et al.* [35] In the prospective, multi-center clinical trial, they compared 61 patients to reach month 12 follow-up with 61 propensity score-matched historical control subjects who received conventional ACDF for single-level cervical degenerative disc disease. Researchers in this study concluded that the simplify disc is better than ACDF from baseline to month 12.

The results of this study also revealed that ADR treatment compared to ACDF treatment had a significant effect on reducing the mean NDI of individuals. In a study, Anna MacDowall *et al.* [36] compared EDR and ACDF surgical treatments. The purpose of this study was comparing the efficacy of ADR surgery with fusion after decompression for the treatment of cervical degenerative disc disease and radiculopathy. Out of 3998 patients infected, 204 had experienced arthroplasty and 3794 had undertaken fusion. The results of this 5-year study showed that there was no important difference in outcomes after 5 years in patients with cervical degenerative disc disease and radiculopathy, and decompression plus ADR surgery, compared with decompression and fusion surgery. Also, in a study by Todd. Lanman *et al.* [37] in 2017, the aim was to evaluate effectiveness among the patients experiencing anterior cervical surgery using the Prestige LP ADR prosthesis to treat degenerative cervical spine disease at two adjacent levels compared with ACDF. To check this, a prospective clinical trial was conducted in US and compared the low-profile titanium ceramic composite-based Prestige LP ADR (n = 209) at two levels with ACDF (n = 188) in 84 months. The result showed that the low-profile artificial cervical disc, Prestige LP, implanted at two adjacent levels, maintains improved clinical outcomes and segmental motion 84 months after surgery and is an effective alternative to fusion.

Conclusion

Different studies have been conducted to assess the effectiveness of surgical treatments in CR treatment. A network meta-analysis was used to determine the best

surgical treatment based on reducing the NDI mean. The most effective surgical treatments for CR were Mobi-c, KineflxC, and ADR compared to ACDF, respectively. It is hoped that the obtained information will provide new insights into the surgical treatments of CR and share good information for physicians to manage and treat CR.

Acknowledgment

The authors greatly appreciated the statistician who participated in this study.

Conflict of interest

The authors stated no conflict of interest.

Funding

This study received no external funding.

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