

## Original Article

# Safety of anterior cervical discectomy and fusion versus cervical arthroplasty in patients with cervical spondylosis: a meta-analysis of randomized controlled trials

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**Abstract:** Anterior approach is widely used for patients with cervical spondylosis. Previous studies suggested that cervical arthroplasty was superior to anterior cervical discectomy and fusion (ACDF). However, the reported incidence of adverse events varied substantially in clinical trials. This study aimed to obtain a better understanding of the risk of adverse events among patients undergoing anterior approach. We searched the PubMed, Embase, and Cochrane Library for relevant studies published prior to Oct 2014, involving patients with cervical spondylosis to compare the safety of ACDF with cervical arthroplasty. Relative risk (RR) was used to measure the safety of ACDF and cervical arthroplasty using random effects model. Twelve trials ( $n = 2,838$ ) that met our inclusion criteria were identified. In a pooled analysis, patients who received ACDF showed a 24% increase in the risk of adverse events when compared with cervical arthroplasty. However, this increase was not associated with statistical significance. Further, there was no significant difference in any specific adverse events between ACDF and cervical arthroplasty. In conclusion, cervical arthroplasty is a safe alternative for patients with cervical spondylosis.

**Keywords:** Anterior, ACDF, arthroplasty, cervical, spondylosis, adverse

## Introduction

Anterior cervical discectomy and fusion (ACDF) is a safe and effective treatment for radiculopathy and myelopathy [1, 2]. However, it also leads to abnormal loading and adjacent level spinal kinematics [3, 4]. Currently, most studies suggest that cervical arthroplasty was beneficial for resolving the complications, resulting in better prognosis, and lower reoperation rates [5-8]. However, the safety of ACDF and cervical arthroplasty were not consistent between studies.

Recently, additional randomized controlled trials of ACDF versus cervical arthroplasty were completed [9-11]. These trials reported inconsistent results of therapies in terms of adverse events, leading to uncertainty over the presence and magnitude of any harmful effects of ACDF versus cervical arthroplasty, and difficulties in interpretation of the results. For a better understanding of the safety of ACDF versus cer-

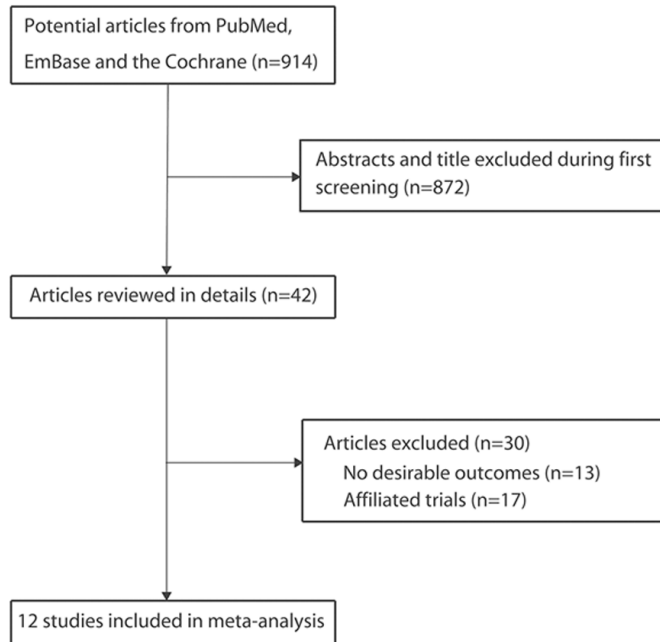
vical arthroplasty, the data from these trials combined with previous trials were re-evaluated. We conducted a systematic review and meta-analysis including the most recent evidence of the safety of ACDF versus cervical arthroplasty in patients with cervical spondylosis.

## Materials and methods

### *Data sources, search strategy, and selection criteria*

This review was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) Statement, issued in 2009 (PRISMA checklist) [12]. We gathered data from randomized controlled trials to evaluate the safety of ACDF compared with cervical arthroplasty on the risk of adverse events. We included trials comparing ACDF with cervical arthroplasty, in order to diminish the systematic and resultant bias, and ensure the reliability of our conclusion.

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**Figure 1.** The flow chart outlines the article selection process.

We systematically searched the literature to identify all the relevant randomized controlled trials regardless of publication status (published, in press, and in progress). Relevant trials were identified with the following procedures: (1) Electronic searches: We searched the Medline, Embase, and the Cochrane Central Register of Controlled Trials for randomized controlled trials of ACDF compared with cervical arthroplasty, using (“Corpectomy” OR “ACDF” OR “anterior cervical discectomy and fusion” OR “anterior decompression and fusion” OR “anterior decompression” OR “ventral decompression” OR “ventral approach” OR “ventral”) AND (“cervical myelopathy” OR “CSM” OR “myelopathy” OR “cervical vertebrae” OR “cervical stenosis”) AND “clinical trial” AND “human” as search terms. All reference lists from reported non-randomized controlled trials were searched manually for additionally eligible studies. (2) Other sources: We contacted authors to obtain possible additional published or unpublished data and searched <http://www.ClinicalTrials.gov> for ongoing randomized controlled trials, which were registered as completed but not yet published using the inclusion criteria above. Medical subject headings, methods, patient population, interventions, and adverse events variables of these studies were used to identify relevant trials.

The literature search, data extraction, and quality assessment were undertaken independently by two authors with a standardized approach, and any discrepancies were settled by group discussion. Studies were eligible for inclusion if: (1) the study was a randomized controlled trial; (2) the number of adverse events occurred during the study; (3) the trials assessed the safety of ACDF versus cervical arthroplasty; (4) patients with cervical spondylosis; and (5) the duration of the follow-up was at least 12 months.

### *Data collection and quality assessment*

All data from eligible trials were independently extracted in duplicate by two independent investigators using the standard protocol and were reviewed by a third investigator. Any discrepancies were resolved by group discussion. Data were extracted from the included trials as follows: name of first author or study group, publication years, number of patients, number of males and females, mean age, disease status, intervention, control, duration of follow-up and adverse events. Data entry by one author was reviewed by the primary author. The study quality was assessed using the Jadad score [13], which was based on the five following subscales: randomization (1 or 0), concealment of the treatment allocation (1 or 0), blinding (1 or 0), completeness of followup (1 or 0), and the use of intention-to-treat analysis (1 or 0). A “score system” (ranging from 0 to 5) has been developed for assessment. In our study, we considered a study with a score of 4 or above as a high-quality study.

### *Statistical analysis*

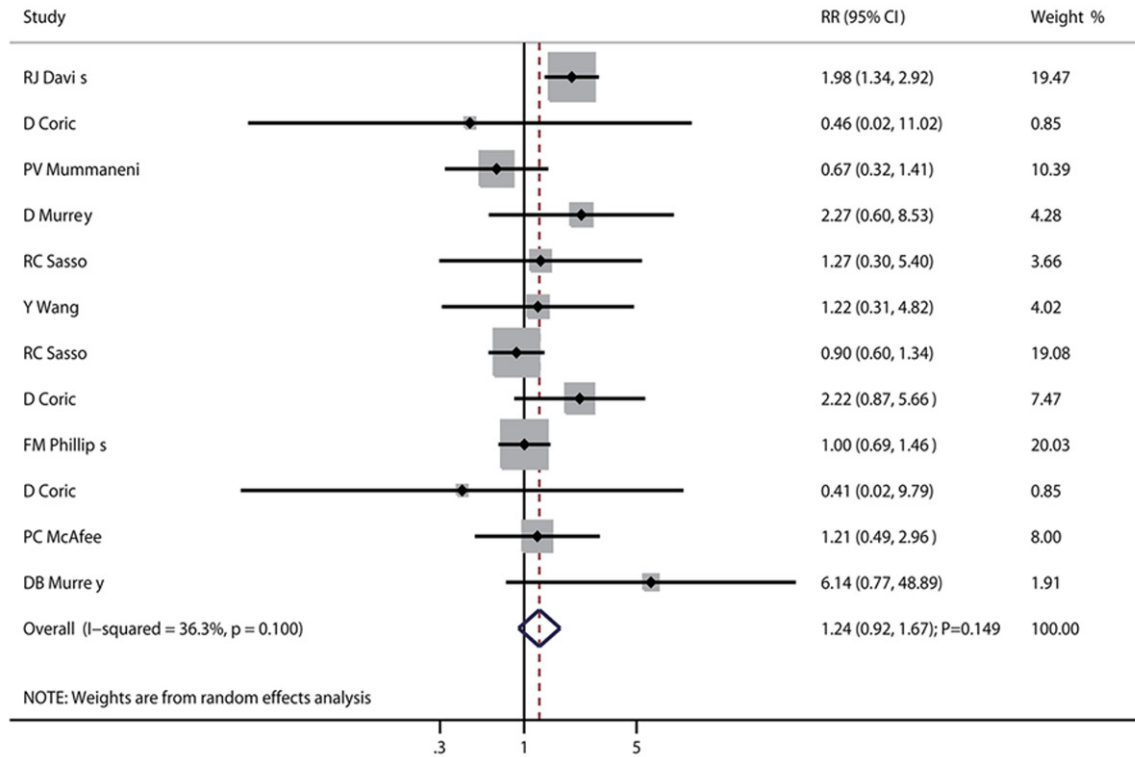
We allocated the results of each randomized controlled trial as dichotomous frequency data. Relative risks (RRs) and 95% confidence intervals within individual study (CIs) were calculated from event numbers that were extracted from each trial before data pooling. The overall RR and 95% CIs of adverse events, and specific categories of adverse events were also calculated. Both fixed-effect and random-effects models were used to assess the pooled RR for

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**Table 1.** Baseline characteristics of studies included in the systematic review and meta-analysis

Study	Publication years	Sample size	Male/female	Mean age	Disease status	Control	Followup duration	Jadad score
RJ Davis	2013	330	158/172	45.6	Two-level symptomatic degenerative disc disease	Mobi-C TDR	2.0 years	3
D Coric	2010	98	38/52	46.4	Single- and 2-level cervical disc disease	Bryan	6.0 years	2
PV Mummaneni	2007	541	250/291	43.6	single-level cervical degenerative disc disease	PRESTIGE ST Cervical Disc System	2.0 years	3
D Murrey	2009	209	95/114	42.8	Single-level symptomatic cervical disc disease	ProDisc-C	2.0 years	1
RC Sasso	2007	115	62/53	44.6	Single-level, symptomatic, cervical radiculopathy or refractory myelopathy	Bryan	2.0 years	3
Y Wang	2008	59	32/27	41.6	Single-level cervical disc disease	Bryan	2.0 years	2
RC Sasso	2011	463	-	-	Single-level cervical disc herniations or spondylosis	Bryan	4.0 years	1
D Coric	2011	269	110/159	43.8	Single-level, symptomatic cervical disc disease	Kineflex C	2.0 years	3
FM Phillips	2013	342	148/194	44.6	Single-level, degenerated cervical disc	PCM	2.0 years	3
D Coric	2013	74	30/43	49.4	Single-level cervical radiculopathy	Bryan Disc and Kineflex C	4.0 years	3
PC McAfee	2010	251	123/128	45.5	Single-level anterior cervical reconstructions	PCM	2.0 years	2
DB Murrey	2007	87	48/39	43.8	Single-level, symptomatic cervical disc disease	Cervical disc replacement	2.0 years	1

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**Figure 2.** The forest plot compares the risk of adverse events with cervical disc arthroplasty and fusion.

**Table 2.** Relative risks of specific adverse events: a summary

Outcomes	Included studies	RR and 95% CI	P value	Heterogeneity (%)	P value for heterogeneity
Anatomy/technical difficulty	2	1.35 (0.26-7.10)	0.73	0	0.33
Dysphagia/dysphonia	5	1.67 (0.97-2.88)	0.06	0	0.69
Gastrointestinal	2	2.06 (0.23-18.59)	0.52	0	0.38
Heterotopic ossification	2	0.40 (0.06-2.47)	0.32	0	0.85
Malpositioned implant	1	0.25 (0.01-4.53)	0.35	-	-
Neck &/or arm pain	2	1.75 (0.51-6.01)	0.37	22.0	0.26
Neurological	2	1.30 (0.08-21.78)	0.85	84.0	0.01
Respiratory	2	0.51 (0.05-4.85)	0.56	0	0.74
Infection	2	0.87 (0.20-3.79)	0.86	16.0	0.27
Vessel injury	1	0.52 (0.05-5.71)	0.59	-	-
Other pain	2	0.98 (0.33-2.95)	0.97	0	0.94
Other	2	2.54 (0.26-24.58)	0.42	41.0	0.19

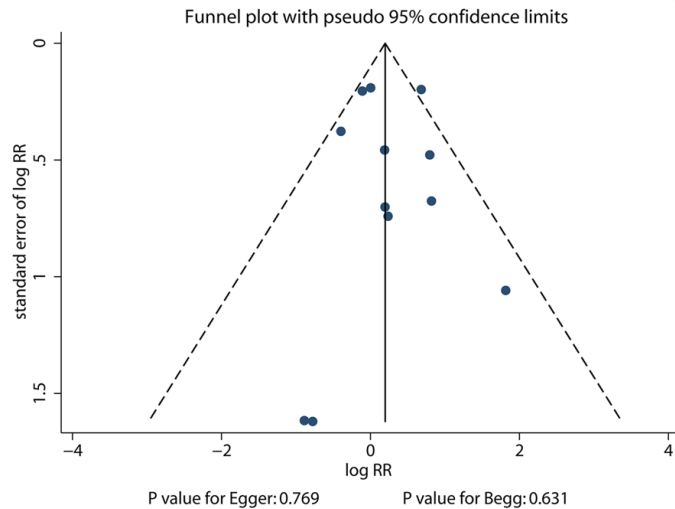
ACDF versus cervical arthroplasty. Although both models yielded similar findings, results from the random-effects model presented here assumed that the true underlying effect varied among included trials [14, 15]. Heterogeneity of the treatment effects between studies was investigated visually by a scatter plot analysis as well as statistically using the heterogeneity  $I^2$  statistic [16, 17]. We also performed a sensitivity analysis by removing each individual trial from the meta-analysis [18]. Egger [19] and

Begg [20] tests were used to check for potential publication bias. All the reported  $P$  values were two-sided and value of  $P$  less than 0.05 was regarded as statistically significant for all included studies. All analyses were calculated using software STATA (version 10.0).

### Results

Of the 42 trials retrieved for detailed assessment, 30 were excluded for lack of data involv-

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**Figure 3.** Funnel plot of adverse events.

ing adverse events or reporting similar study population. Our final analysis included 12 randomized controlled trials [9-11, 21-29], consisting of 2,838 patients with cervical spondylosis (**Figure 1**). These trials compared ACDF versus cervical arthroplasty and reported adverse events as the endpoints. **Table 1** summarizes the characteristics of these trials and important baseline data of the included 2,838 patients. The number of patients ranged from 59 to 541. The duration of follow-up ranged from 2.0 to 6.0 years. We included only those randomized controlled trials with the number of patients exceeding 50 to ensure that high-quality literature was included in our study. Although the included trials scarcely reported the key indicators of trial quality, the quality of the included trials was also evaluated according to pre-defined criteria using the Jadad score [13]. Overall, six of the included trials [9-11, 22, 24, 27] scored 3, three trials [21, 25, 28] scored 2, and the remaining three trials [23, 26, 29] scored 1.

Data supporting the harmful effects of ACDF were available from 12 trials [9-11, 21-29], including 2,885 patients and 340 adverse events. Overall, ACDF therapy resulted in a 24% increase in the risk of adverse events compared with cervical arthroplasty (RR, 1.24; 95% CI: 0.92-1.67;  $P = 0.149$ , **Figure 2**). Although there was some evidence of heterogeneity across the studies included, sensitivity analysis indicated that the results were not affected by sequential exclusion of any particular trial from all pooled analysis. Further, sensitivity analysis suggested that ACDF therapy was not associ-

ated with the risk of adverse events when compared with cervical arthroplasty after excluding two trials conducted by RJ Davis et al [9], and D Coric et al [21] (RR: 1.04; 95% CI: 0.83-1.32;  $P = 0.713$ ; I-square: 1.4%;  $P$  value for heterogeneity: 0.425), which specifically included patients with two-level degenerative disc disease.

We noted that specific adverse events were reported by a few trials. Therefore, we provided a summary of the relative risks of specific adverse events in **Table 2**. No significant differences were identified between the safety of ACDF and cervical arthroplasty.

A review of the funnel plots did not rule out potential publication bias for adverse events (**Figure 3**). However, the Egger [19] and Begg tests [20] showed no evidence of publication bias for adverse events ( $P$  value for Egger: 0.769;  $P$  value for Begg: 0.631).

### Discussion

Although ACDF has been considered the gold standard for the treatment of cervical spondylosis for a few decades, evidence from several randomized controlled trials supports cervical arthroplasty as an alternative therapy. The results of our meta-analysis showed that the safety of patients undergoing ACDF and cervical arthroplasty was not statistically significant. Further, no significant difference was observed between ACDF and cervical arthroplasty for specific adverse events.

Several systematic reviews and meta-analyses [30, 31] evaluated the efficacy of ACDF versus cervical arthroplasty and found that cervical arthroplasty were superior or equivalent to ACDF. However, the safety of ACDF versus cervical arthroplasty has not been concluded. According to Davis' trial [9], cervical arthroplasty significantly reduced the risk of adverse events when compared with ACDF. However, most studies reported inconsistent results. Our study was also inconsistent with this randomized controlled trial, probably due to the inclusion of patients with 2-level symptomatic degenerative disc disease. Most studies included the reported adverse events approximately. Nonetheless, our current study restricted the

duration of the followup to at least 12 months and reviewed long-term outcomes post-surgery to ensure reliability.

In 2010, Coric *et al* [21] suggested no significant difference in adverse events between ACDF and cervical arthroplasty probably because the study reported only 1 patient with dysphagia in cervical arthroplasty group. Furthermore, the study conducted by Coric *et al.* in 2011 [27] suggested that Kineflex|C CTDR might play an important role in the risk for dysphagia. In our current study, we also conducted pooled analyses of specific adverse events. However, data related to specific adverse events were rarely available in these trials. Nonetheless, we also provided a comprehensive result by comparing ACDF with cervical arthroplasty for specific adverse events and listed in **Table 2**. Further large-scale randomized controlled trials need to be analyzed for safety.

Several strengths of our study should be highlighted. First, systematic reviews and meta-analyses are the most powerful tools to assess inconsistencies. Second, patients included in our study showed varying baseline disease status, which evaluated the safety of the anterior approach in patients with cervical spondylosis. Third, we restricted our review to randomized controlled trials, and included patients with at least 12 months of follow-up to provide the best evidence.

The study limitation includes the inherent assumptions in any meta-analysis, because the analysis used pooled data from published papers or was provided by individual trial authors. Missing individual patient data and original data prevented detailed analysis for comprehensive results. We also lacked sufficient data for detailed analysis of ACDF versus cervical arthroplasty on the risk of different adverse events. Therefore, we merely provided a relative analysis of ACDF versus cervical arthroplasty and developed a synthetic and comprehensive review.

In conclusion, no significant differences in adverse events were seen between ACDF and cervical arthroplasty, suggesting that cervical arthroplasty was an effective and safe alternative for patients with cervical spondylosis. Furthermore, we suggest that the type of

adverse events should be recorded and reported normatively in future research.

### Disclosure of conflict of interest

None.

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