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REVIEW

Safety and efficacy of cervical disc arthroplasty in preventing the adjacent segment disease: a meta-analysis of mid- to long-term outcomes in prospective, randomized, controlled multicenter studies

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Dariusz Latka[1,2]
Klaudia Kozlowska[3]
Grzegorz Miekisiak[1,2]
Kajetan Latka[2]
Jacek Chowaniec[2]
Tomasz Olbrycht[2]
Miroslaw Latka[3]

[1]Department of Anatomy, Institute of Medicine, University of Opole, Opole, Poland; [2]Department of Neurosurgery, University Hospital in Opole, Opole, Poland; [3]Department of Bioengineering, Institute of Biomedical Engineering, Technical University of Wroclaw, Wroclaw, Poland

Objectives: Cervical disc arthroplasty (CDA) has become an alternative treatment for cervical radiculopathy and myelopathy. This technique preserves appropriate motion at both the index and adjacent disc levels and consequently may prevent adjacent segment degeneration (ASD). The authors performed a meta-analysis to compare the safety and efficacy of CDA to those of the gold standard, anterior cervical discectomy and fusion (ACDF). Both surgical and clinical parameters were employed to verify the hypothesis that CDA can reduce the risk of ASD.

Methods: The meta-analysis comprised high-quality randomized controlled trials that compared CDA and ACDF treatments of cervical degenerative disc disease. Included papers reported data for at least one of the following outcomes: 1) surgical parameters, 2) questionnaire clinical indices (pre- and postoperative values), and 3) complication rates at 24 months; in addition, for ASD we analyzed 60 month or longer follow-ups. We used mean differences (MDs) or ORs to compare treatment effects between CDA and ACDF.

Results: Twenty studies with 3,656 patients (2,140 with CDA and 1,516 with ACDF) met the inclusion criteria. CDA surgery, with mean duration longer than that of ACDF, was associated with higher blood loss. Visual analog scale neck pain score was significantly smaller for CDA (mean difference =–2.30, 95% CI [–3.72; –0.87], P=0.002). The frequency of dysphagia/dysphonia (OR =0.69, 95% CI [0.49; 0.98], P=0.04) as well as the long-term ASD rate for CDA was significantly smaller (OR =0.33, 95% CI [0.21; 0.50], $P<0.0001$).

Conclusion: A significantly lower probability of ASD reoperations in the CDA cohort after a 60-month or longer follow-up was the most important finding of this study. Despite the moderate quality of this evidence, the pooled data corroborated for the very first time that CDA was efficacious in preventing ASD.

Keywords: cervical disc arthroplasty, CDA, anterior cervical discectomy and fusion, ACDF, cervical degenerative disc disease, CDDD, meta-analysis, randomized controlled trial, RCT, cervical total disc replacement, CTDR

Correspondence: Dariusz Latka
Department of Neurosurgery, University Hospital in Opole, Al.Witosa 26, Opole 45-418, Poland
Tel +48 774 552 0724
Fax +48 774 552 0724
Email dlatka@mp.pl

Introduction

Cervical degenerative disc disease (CDDD) has become a civilization disease and one of the significant causes of work-related disability.[1] In the case of conservative treatment failure, surgery is the only alternative. For many decades, anterior cervical discectomy and fusion (ACDF) has been regarded as the gold standard. However, an analysis of

long-term treatment results indicates that over 90% of patients who undergo ACDF develop significant degenerative changes in the adjacent spinal segments.[2,3] Almost one-quarter of these changes are symptomatic and require surgery within a decade. The rate of reoperation is equal to 2.9% level/year.[4] Degeneration may occur in its natural course but segment stiffening may exacerbate it. Clinical observations, especially in adolescent groups (traumatic fusions or Klippel-Feil syndrome) in which degeneration resulting from natural history is unlikely, indicate that stiffening may be a fundamental pathogenic factor causing degeneration of neighboring segments.[5] Clinical evidence has led to the formulation of the concept of adjacent segment degeneration (ASD). The development of cervical disc arthroplasty (CDA) was driven by the expectations that preservation of motion at both index and adjacent disc levels would minimize the ASD risk. To some extent, these expectations were fueled by the success of hip joint arthroplasty, which replaced arthrodesis in the treatment of severe coxarthrosis.

Aims

Advantages and disadvantages of ACDF and CDA have been analyzed in several previous publications.[6–12] The authors decided to design a meta-analysis that would assess the safety of both the methods and elucidate their long-term efficacy in ASD prevention.

Materials and methods

Search strategy

The neurosurgeons independently carried out a comprehensive Internet literature search of the following English databases: PubMed, Medline, EMBASE, Cochrane Central Register of Controlled Trials – Issue 1, 2016 – Scopus, OvidSP, and Google Scholar. The queries were last updated in February 2018. The search terms contained a combination of the following keywords: "cervical arthroplasty," "cervical disc replacement," "total disc replacement," "anterior cervical fusion," "CDA," "TDR," "TDA," "ACDF."

Study selection

The first stage of selection was based on the publication's title and screening of its abstract. The reviewers then independently assessed the eligibility of the content of the article. Any disagreement was resolved through discussion. All papers non-compliant with the recommendations contained in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA-P checklist; Supplementary materials), duplicates, and studies with incomplete data were excluded from further analysis.[13]

Eligibility criteria

The inclusion criteria consisted of several parameters: 1) the publication was an English description of a prospective, controlled, multicenter, randomized controlled trial (RCT), and reported data of at least 2-year follow-up; 2) the publication compared the outcomes of ACDF and CDA treatments of patients over 18 years of age (regardless of gender) at one or two levels of the spine with radiculopathy and/or myelopathy; 3) clinical evaluation included at least one of the following indicators: neck disability index (NDI), visual analog scale (VAS) for neck and/or arm pain, reoperation rate at the operated and adjacent levels, surgical parameters (blood loss, surgery time, and hospital stay), and rate of adverse effects.

Data collection

Each paper was described using author, year of publication, country of origin, number of operating centers, number of CDA and ACDF groups, type of CDA prosthesis, number of implantation levels, and a period of observation. Some of the studies were extensions beyond the original observation period.

Quality of evidence assessment and risk of bias

The risk of bias was assessed with a six-item scale recommended by the Cochrane Back Review Group.[13,14] We used the following appraisal parameters: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of results assessor, incomplete data, and selective result reporting. Risk of bias in all areas was defined as low, high, or unclear. The quality of evidence for each outcome was rated according to the Grades of Recommendation, Assessment, Development, and Evaluation approach. Several study criteria were assessed: design, quality, consistency, and directness. Publication bias was assessed using funnel plots.

Extraction of summary measures

Differences in treatment effects between CDA and ACDF were estimated using mean difference (MD) and its 95% CI for continuous measures or OR and its 95% CI for dichotomous measures (rate CDA/ACDF). The following outcome measures were used: surgical parameters (operation time, blood loss, and length of hospital stay), NDI, VAS for neck and arm, and complication rates (number of adverse events, adjacent segment disease, and reoperations at the index level). For questionnaire clinical indices, we compared postoperative values in addition to differences between pre- and

postoperative values. Both dichotomous and continuous parameters were compared 24 months after the operation. In addition, the OR of reoperations due to ASD was calculated for 60 months or longer follow-ups.

Statistical analysis

The data analysis was performed using R (version 3.3.2; https://www.r-project.org/) and a "meta" package using a fixed-effects model.[15] The chi-squared and Higgin's I^2 tests were used to evaluate heterogeneity across studies.

Cut-off values of 25%, 50%, and 75% were used to label heterogeneity as low, moderate, or high, respectively.[16] If I^2 was >50%, a subgroup analysis was attempted with respect to the type of prosthesis and/or the number of implantation levels in order to find the source of heterogeneity. The significance threshold for all statistical tests was set to 0.05.

Supplementary data

The forest plots of the following parameters determined at 24 months are available in Supplementary materials: operative time, hospital stay, blood loss, NDI, VAS neck and arm pain scores, adjacent segment disease, reoperations at index level, adverse effects, dysphagia/dysphonia. The supplementary data also include the forest plot of changes in NDI and VAS neck and arm pain scores over 24 months.

Results

Study search and characteristics

Twenty articles with 3,656 patients and nine types of prostheses (2,140 with CDA and 1,516 with ACDF) met the inclusion criteria. The follow-up duration in every study was at least 24 months. Four studies reported outcomes for 60 months and four up to 84 months. Figure 1 illustrates the

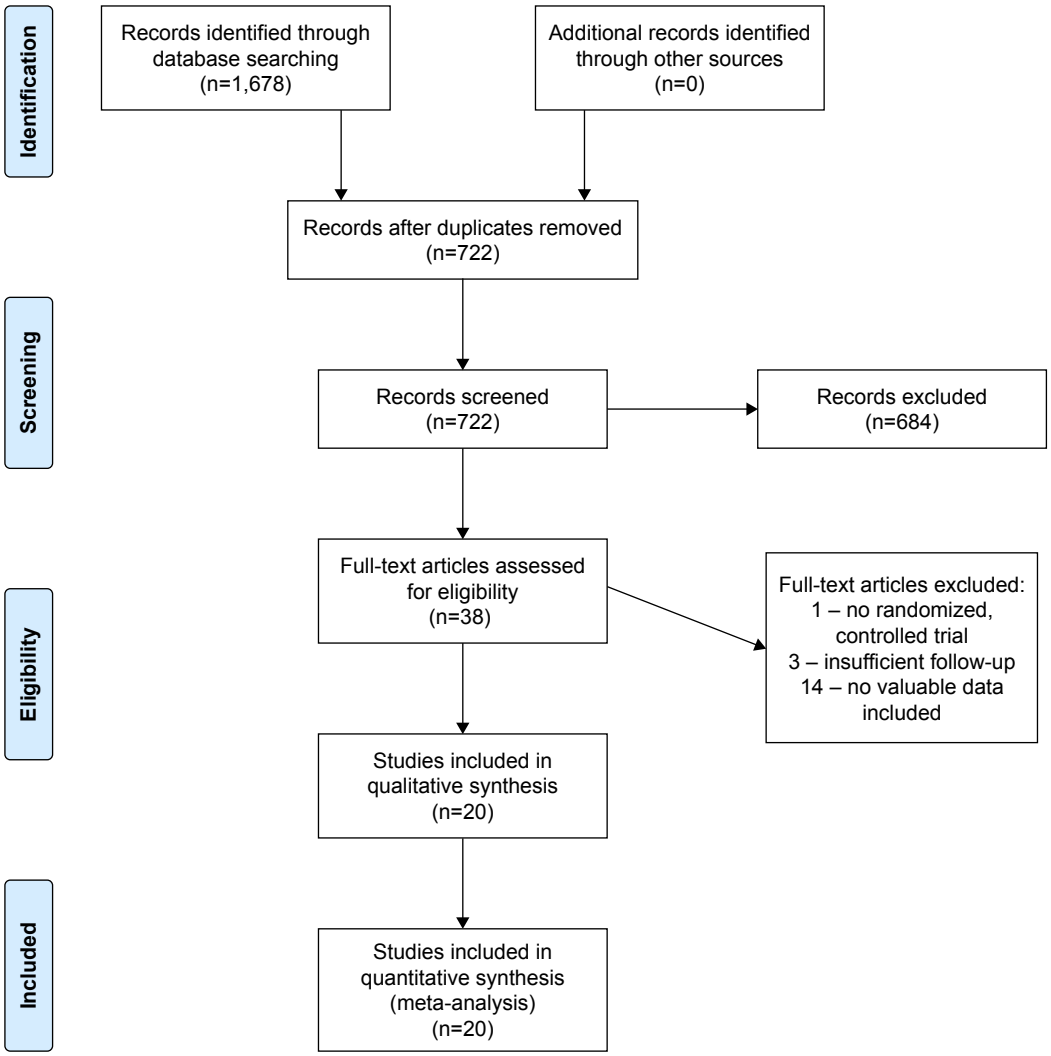

Figure 1 Flowchart of study selection.

study selection process. Figure 2 presents study and patient characteristics.

Risk of bias

In the majority of papers, the risk of bias was unclear or low. In four articles, the number of low-risk points was at least equal to unclear points. At least one point of high risk of bias was marked in four papers. Figure 3 summarizes the assessment of risk of bias.

Analysis of surgical parameters

Nine studies with 2,353 patients (CDA =1,302, ACDF =1,051) were pooled to evaluate operative time of two surgical techniques. The mean operative time for ACDF was significantly shorter than that for CDA (MD =0.23, 95% CI [0.09; 0.36], $P<0.001$; $I^2=83.56\%$; 95% CI [70.33%; 90.89%]) (Figure S1). Subgroup with the Mobi-C prothesis could be a potential source of high heterogeneity ($I^2=57.0\%$). Furthermore, there were significant differences between subgroups

	Author	Year	Implant	Centers	CDA/ACDF	Follow-up (months)
1	Heller et al[44]	2009	Bryan	30 USA	242/221	24
2	Sasso et al[45]	2011	Bryan	30 USA	242/221	48
3	Zhang et al[46]	2012	Bryan	3 CHINA	60/60	24
4	Mummaneni et al[47]	2007	Prestige ST	32 USA	276/265*	24
5	Burkus et al[48]	2014	Prestige ST	32 USA	276/265*	60
6	Murrey et al[49]	2009	ProDisc C	13 USA	103/106	24
7	Zigler et al[50]	2013	ProDisc C	13 USA	103/106	60
8	Janssen et al[51]	2015	ProDisc C	13 USA	103/106	84
9	Coric et al[52]	2011	Kineflex C	21 USA	136/133	24
10	Vaccarro et al[53]	2013	Secure C	18 USA	151/140	24
11	Hisey et al[54]	2016	Mobi-C	23 USA	164/81	60
12	Davis et al[55]	2015	2L Mobi-C	24 USA	225/105	48
13	Radcliff et al[56]	2016	2L Mobi-C	24 USA	225/105	60
14	Jackson et al[57]	2016	Mobi-C 2L Mobi-C	24 USA	179/81** 234/105**	60
15	Gornet et al[58]	2015	Prestige LP	20 USA	280/265*	24
16	Gornet et al[59]	2016	Prestige LP	20 USA	280/265*	84
17	Gornet et al[60]	2017	2L Prestige LP	30 USA	209/188	24
18	Phillips et al[61]	2013	PCM	3 USA	189/153	24
19	Phillips et al[62]	2015	PCM	3 USA	189/153	84
20	Skeppholm et al[63]	2015	Discover	3 SWEDEN	81/70	24
					2,140/1,516	

Figure 2 The list of publications included in this meta-analysis.
Note: *The same control group; **the same control group and study enlarged by 15 (1L) i9 (2L).
Abbreviations: ACDF, anterior cervical discectomy and fusion; CDA, cervical disc arthroplasty.

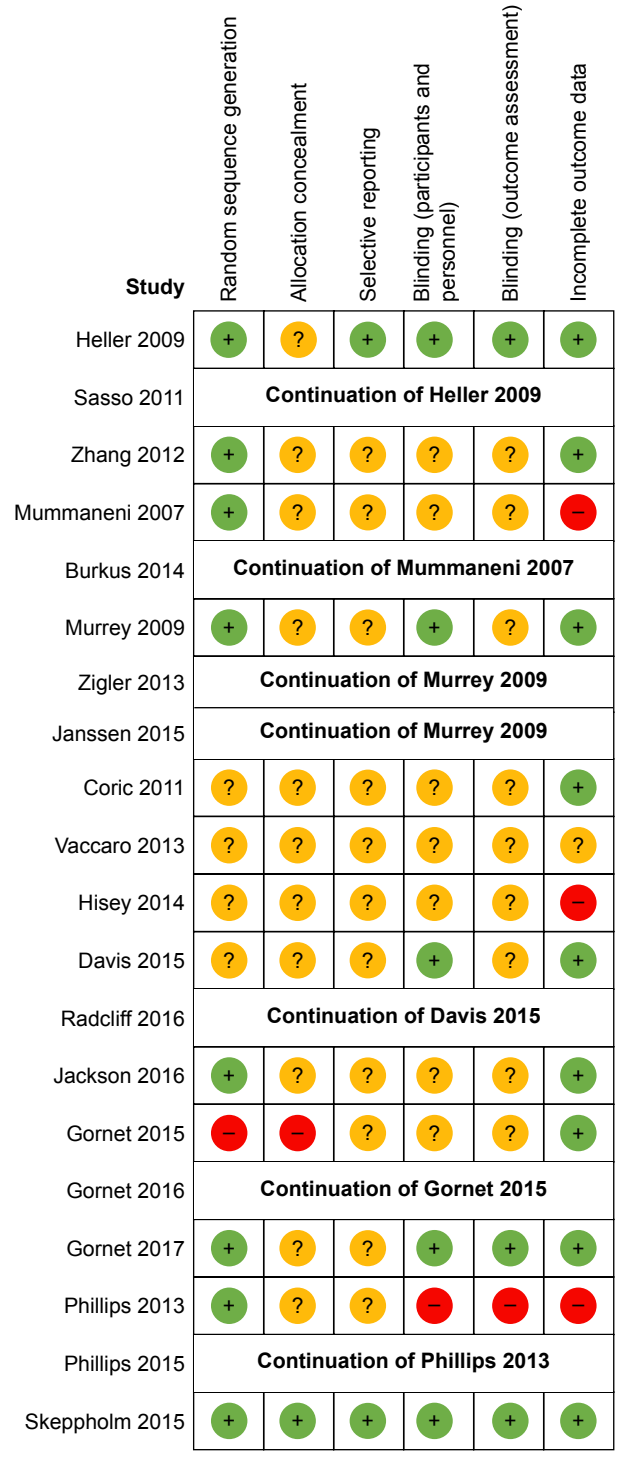

Figure 3 Risk of bias assessment: + low, – high, ? unclear.

($P<0.001$). The asymmetry of funnel plot was not observed. The quality of this evidence was moderate.

There was no significant difference in length of hospital stay between CDA and ACDF groups (MD =–0.92, 95% CI [–0.11; 0.08], $P=0.05$, $I^2=49.78\%$, 95% CI [0.0%; 77.58%]) (Figure S2). The comparison was based on eight studies with 2,202 patients (CDA =1,221, ACDF =981).

Asymmetry in the funnel plot was not observed. Subgroup analysis based on type of prosthesis revealed statistically significant differences ($P=0.02$). However, the analysis did not identify the source of heterogeneity. The quality of this evidence was very low.

Nine studies with 2,778 patients (CDA =1,522, ACDF =1,256) provided data for blood loss. The blood loss for ACDF was significantly lower than that of CDA (MD =9.23, 95% CI [5.35; 13.12], $P<0.0001$, $I^2=1.54\%$, 95% CI [0.0%; 65.34%]) (Figure S3). There was no asymmetry in the funnel plot, and the quality of this evidence was moderate.

Analysis of clinical parameters at 24 months

Five studies with 1,635 patients (CDA =843, ACDF =792) reported data for NDI scores at 24 months. NDI scores were lower in CDA group, albeit the quality of evidence was low (MD =–0.85, 95% CI [–1.89; 0.18], $P=0.11$, $I^2=0.0\%$, 95% CI [0.0%; 66.73%]) (Figure S4). The source of heterogeneity was unknown. The funnel plot was symmetrical.

Four studies with 1,426 patients (CDA =740, ACDF =686) presented data for VAS neck pain score at the 24-month follow-up. The score for CDA was significantly lower than that of ACDF (MD =–2.30, 95% CI [–3.72; –0.87], $P=0.002$, $I^2=0.0\%$, 95% CI [0.0%; 74.96%]) (Figure S5). The source of heterogeneity was unknown. The asymmetry of funnel plot was not observed. The quality of this evidence was moderate.

The outcome of four studies comprising 1,426 patients (CDA =740, ACDF =686) showed that VAS arm pain score was lower for CDA (MD =–1.05, 95% CI [–2.41; 0.30], $P=0.13$, $I^2=0.0\%$, 95% CI [0.0%; 0.0%]) (Figure S6). The source of heterogeneity was unknown. The funnel plot was symmetrical. The quality of this evidence was low.

The meta-analysis of ten studies with 3,844 patients (CDA =2,021, ACDF =1,823) showed that patients who undergo CDA are at lower risk, statistically non-significant, to develop ASD in comparison with those who undergo ACDF (OR =0.68, 95% CI [0.44; 1.05], $P=0.08$, $I^2=5.76\%$, 95% CI [0.0%; 69.44%]) (Figure S7). The source of heterogeneity was unknown. The asymmetry of funnel plot was not observed. The quality of this evidence was low.

Eight studies with 2,921 patients (CDA =1,556, ACDF =1,365) were pooled to evaluate rate of reoperations at index level. Patients who undergo CDA are at statistically non-significant lower risk to undergo reoperation in

comparison with those who undergo ACDF (OR =0.66, 95% CI [0.41; 1.06], *P*=0.09, I^2=0.0%, 95% CI [0.0%; 60.39%]) (Figure S8), with a moderate quality of evidence. The source of heterogeneity was unknown. The funnel plot was symmetric.

Twelve studies with 4,383 patients (CDA =2,349, ACDF =2,034) provided data for adverse effects. There was no significant difference in risk for both groups (OR =0.87, 95% CI [0.56; 1.35], *P*=0.54, I^2=75.23%, 95% CI [53.90%; 86.70%]) (Figure S9). Subgroup analysis with respect to type of prosthesis did not reveal the source of heterogeneity. The asymmetry of funnel plot was absent.

Nine studies with 3,369 patients (CDA =1,815, ACDF =1,554) reported the rate of dysphagia/dysphonia. Patients who undergo CDA are at a statistically significant lower risk for developing dysphagia/dysphonia in comparison with those who undergo ACDF. The OR for this parameter was significantly lower in the CDA group (OR =0.69, 95% CI [0.49; 0.98], *P*=0.04, I^2=0.0%, 95% CI [0.0%; 57.38%]) (Figure S10). The source of heterogeneity was unknown. The asymmetry of funnel plot was not observed. The quality of this evidence was moderate.

Analysis of changes of clinical parameters

Differences in NDI score before and after surgery (24-month follow-up) were evaluated using data from four studies with 1,122 patients (CDA =630, ACDF =492). The difference in NDI score was higher in the CDA cohort (MD =2.64, 95% CI [−1.82; 7.10], *P*=0.25, I^2=80.94%, 95% CI [50.08%; 92.72%]) (Figure S11). The source of high heterogeneity was the subgroup with Bryan prosthesis (I^2=86.50%). The asymmetry of funnel plot was not observed. The quality of this evidence was very low.

Three studies with 659 patients (CDA =388, ACDF =271) reported data for differences in VAS neck pain score before and after surgery (24-month follow-up). The difference in VAS neck pain scores was higher in CDA cohort group (MD =1.75, 95% CI [−0.93; 4.42], *P*=0.20, I^2=0.0%, 95% CI [0.0%; 0.0%]) (Figure S12). The source of heterogeneity was unknown. The funnel plot was symmetric. The quality of this evidence was low.

The data from three studies with 659 patients (CDA =388, ACDF =271) showed that difference in VAS neck pain score was higher in ACDF (MD =−0.29, 95% CI [−2.73; 2.16], *P*=0.82, I^2=0.0%, 95% CI [0.0%; 0.0%]) (Figure S13). The source of heterogeneity was unknown. An asymmetric funnel plot was not observed. The quality of this evidence was very low.

Analysis of ASD over 60 months

Five studies with 1,594 patients (CDA =956, ACDF =638) were pooled to evaluate the rate of ASD of two surgical techniques over a long-term observation. Patients who undergo CDA are at a statistically significant lower risk for developing ASD in comparison with those who undergo ACDF (OR =0.33, 95% CI [0.21; 0.50], *P*<0.0001, I^2=0.0%, 95% CI [0.0%; 58.71%], Figure 4) with a moderate quality of supporting evidence. The source of heterogeneity was unknown. The asymmetry of funnel plot was not observed.

Discussion

ACDF is a treatment of choice for CDDD.[17] According to Cochrane Back and Neck, the creator of spine disease treatment standards, CDA is a viable alternative to ACDF, but it is not always the best treatment option.[18] It is worth pointing out that ACDF leads to reduction in the range of motion at the site of spondylodesis and increased mobility at adjacent levels. Goffin et al used radiographic evidence from long-term observations of ACDF patients and demonstrated that degenerative changes at the level adjacent to the fusion occurred in as many as 92% of patients.[2,19] Preservation of segmental movement at the indexed level was the design

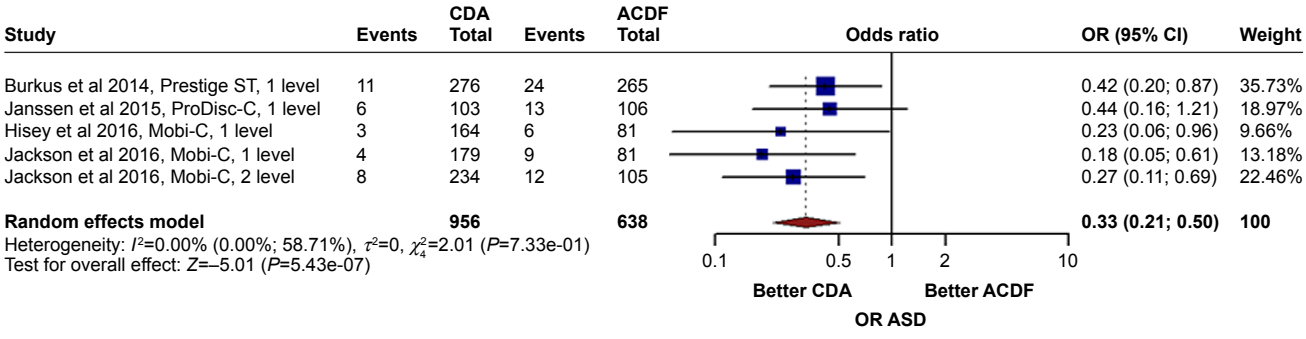

Figure 4 Forest plot of ASD at 60 months.
Abbreviations: ACDF, anterior cervical discectomy and fusion; ASD, adjacent segment degeneration; CDA, cervical disc arthroplasty.

principle of CDA. It was believed that mobility would reduce ASD occurrence due to protection of adjacent segments from mechanical overload.[20] The pathological consequences of such overload cannot be detected by RCTs with short or medium follow-up which make up majority of published studies.[6–12,21–38] The most important meta-analyses concerning efficacy of CDA included only RCTs published before 2012.[32,34,35] The rationale for this meta-analysis was the inclusion of the most recent RCTs with emphasis on long-term follow-up (60 months or longer).

The significantly lower probability of ASD reoperations in the CDA cohort after a 60-month follow-up is the most important study finding. Even though the quality of evidence is moderate, the pooled data corroborate for the very first time that CDA is efficacious in preventing ASD; these results contradict those from some earlier studies. Nunley et al showed that after 36 months, ASD risks after CDA and ACDF surgeries were equal.[39] Therefore, it was hypothesized that some other factors could affect the occurrence of degeneration of the neighboring segment; these other factors include bone mineral density and the presence of co-existing degenerative changes in the lumbar spine. Verma et al also did not find significant differences in the frequency of ASD between CDA and ACDF.[40] However, in their study, only the reoperation index without radiographic assessment was used to calculate ASD frequency. The results of their analysis could be affected by a significantly higher loss of patients in ACDF group during the follow-up period.

It is worth pointing out that the frequency of postoperative dysphagia/dysphonia was significantly lower in patients with mobile devices, which is at variance with the study published last year.[36] Both the number of secondary surgical interventions at the index level and adverse events (excluding dysphagia/dysphonia) in CDA and ACDF groups were not statistically different, in agreement with the results of the previous studies.[6,11,26,36,41] This is interesting because the previous generations of CDA prostheses (such as Bristol-Cummins) were known to cause subluxation, screw damage, and dysphagia.[42] The recent advances in implant technology pave the way for improvement of safety and efficacy of CDA. In particular, modern implants are capable of maintaining optimal motion, disk height, and lordosis. They have also a longer life, cause less inflammation or osteolysis, and better mimic the function of natural intervertebral discs.[43] The potential advantages of modern implants must be verified by RCTs.

It comes as no surprise that this meta-analysis corroborated that the length of CDA surgery was longer than that of ACDF and was associated with greater blood loss. The longer traction on soft neck structures is an apparent disadvantage of CDA.

There are several limitations to this meta-analysis: 1) the review was restricted to papers published in English; 2) studies included in the meta-analysis involved 1- or 2-level CDAs and nine different types of prostheses; 3) the small number of included studies in some meta-analyses; and 4) the quality of evidence varied from very low to moderate.

Conclusion

The most important finding of this study is the significantly lower probability of ASD reoperations in the CDA cohort after a 60-month follow-up. Despite the moderate quality of this evidence, the pooled data corroborated for the very first time that CDA is efficacious in preventing ASD; these results contradict those from some earlier studies. At present, both the number of secondary surgical interventions at the index level and adverse events in CDA and ACDF are comparable. Due to ongoing improvements in implant technology, further RCTs are required to identify patients who could benefit from CDA treatment as well as practical clinical trials, which are specifically designed to confirm the proper indications for CDA, because it is clear that only a defined subset of patients requiring cervical surgery are valid candidates for disc arthroplasty.

Author contributions

All authors contributed toward data analysis, drafting, and critically revising the paper, gave final approval of the version to be published, and agreed to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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