Spine

SPINE Volume 36, Number 25, pp E1623–E1633

Artificial Cervical Disc Arthroplasty

A Systematic Review

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Study Design. Systematic Review.

Objective. (1) To qualitatively analyze the literature on the efficacy and effectiveness of artificial cervical disc arthroplasty (ACDA). (2) To highlight methodological and reporting issues of randomized controlled trials (RCT) reports on effectiveness of ACDA compared to cervical fusion.

Summary of Background Data. ACDA is an alternate surgical procedure that may replace cervical fusion in selected patients suffering from cervical degenerative disc disease.

Methods. We searched seven electronic databases, including MEDLINE, Cochrane Library, and EMBASE, unpublished sources, and reference lists for studies on the efficacy and effectiveness of ACDA compared to cervical fusion—the surgical standard of care for patients with cervical degenerative disc disease.

Results. A total of 622 studies were retrieved, of which 18 (13 case series, four RCT reports, one nonrandomized comparative study) met the inclusion criteria for this review. The four RCTs and the nonrandomized comparative study concluded that the effectiveness of ACDA is not inferior to that of cervical fusion in the short term (up to 2-yr follow-up). The safety profile of both procedures appears similar. The case series reviewed noted improved clinical outcomes at 1 or 2 years after one or multiple-level ACDA.

Conclusion. ACDA is a surgical procedure that may replace cervical fusion in selected patients suffering from cervical degenerative disc disease. Within 2 years of follow-up, the effectiveness of ACDA appears similar to that of cervical fusion. Weak evidence exists that ACDA may be superior to fusion for treating neck and arm pain. Future studies should report change scores and change score variance in accordance with RCT guidelines, in order to strengthen credibility of conclusions and to facilitate meta-analyses of studies.

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Acknowledgment date: September 28, 2010. Revised date: December 24, 2010. Accepted date: January 24, 2011.

The manuscript submitted does not contain information about medical device(s)/drug(s).

Other funds were received in support of this work. No benefits in any form have been or will be received from a commercial party related directly or indirectly to the subject of this manuscript.

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DOI: 10.1097/BRS.0b013e3182163814

Key words: cervical spine, artificial disc, arthroplasty.
Spine 2011;36:E1623–E1633

Anterior cervical discectomy and fusion (ACDF) is the current and considered the definitive surgical treatment for symptomatic, single-level, cervical degenerative disc disease (DDD).[1,2] Symptoms of cervical DDD include neck and arm pain associated with radiculopathy or myelopathy, respectively. Untreated, the signs and symptoms of cervical DDD may decrease, stabilize, or worsen. Initial conservative, noninvasive therapies aim to relieve pain and prevent permanent injury to the spinal cord and nerve roots. Typically, if at least 2 to 6 months of conservative treatment is ineffective, or the patient becomes unable to perform activities of daily living, surgical intervention is indicated.[3]

Following ACDF, DDD is relieved through a combination of decompression and by eliminating movement in the symptomatic motion segment. The procedure involves the use of either autograft or allograft bone placed in the intervertebral space to stimulate the fusion between the vertebral endplates—both methods being associated with additional risks for patients.[4,5] Moreover, fusion alters the normal biomechanics of the spine, which may result in the acceleration of the adjacent-level disease and the need for subsequent reoperation.

Artificial cervical disc arthroplasty (ACDA) is an alternate surgical procedure that may replace cervical fusion in selected patients suffering from cervical DDD. The goals of disc arthroplasty are to restore the intervertebral disc and foraminal height so as to prevent recurrence of nerve root compression.[6,7] Preserving physiological range of motion, rather than fusing the degenerative spine, may limit the segmental progression of disease that affects many patients.

The results of the first human trial in which a cervical prosthesis (Cummins-Bristol) was used were reported in 1998.[8] The new Frenchay cervical disc replaced the lower component of the Cummins joint. Later, the Frenchay cervical disc was renamed Prestige cervical disc.[8] In contrast to the metal-on-metal design of the Cummins-Bristol disc, a metal-on-plastic design called the Bryan disc emerged by the late 1990s.[8] Along the same lines as the metal-on-plastic concept, the Porous Coated Motion (PCM) artificial disc was developed recently with two different designs to address the integrity of the posterior longitudinal ligament after cervical

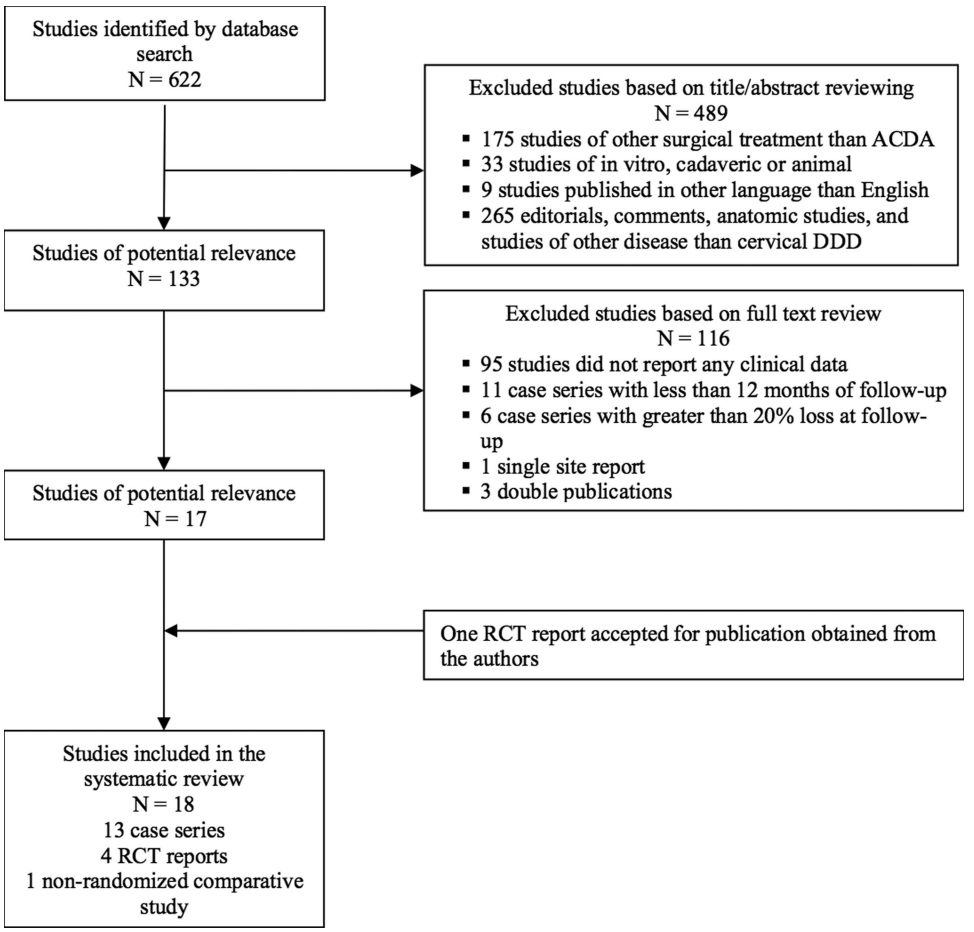

Figure 1. The systematic review flow.

decompression.[8] Another disc replacement that has been used in Europe since 1990 is the ProDisc-C.[8] Other arthroplasty devices are actively being developed and tested and will likely emerge in the coming years (such as the Maverick disc, Medtronic Sofamor Danek, Memphis, Tenn; Flexcore, Stryker Spine, Kalamazoo, MI).[9]

This systematic literature review was based on the following objectives: (1) to qualitatively analyze the literature on the efficacy and effectiveness of ACDA and (2) to highlight methodological and reporting issues of randomized controlled trials (RCT) reports on effectiveness of ACDA compared to cervical fusion.

MATERIALS AND METHODS

The search comprised seven databases, unpublished sources, and reference lists for studies on the efficacy and effectiveness of ACDA compared to cervical fusion. The databases searched were MEDLINE (OVID), Cochrane CENTRAL Register of Controlled Trials (OVID 4th Quarter), Cochrane Database of Systematic Reviews (OVID 4th Quarter), Health Technology Assessment Database (OVID 4th Quarter), DARE Database of Reviews of Effects (OVID 4th Quarter), NHS Economic Evaluation Database, and EconLit (EBSCO) database. The search strategies used for each of these databases are presented in Appendix 1 (see Appendix 1, Supplemental Digital Content 1, http://links.lww.com/BRS/A572). Our searches were limited to the last 10 years (1998–2008), English language, and human studies. We also manually searched the reference lists of the included studies and, where possible, contacted authors and industry in an effort to obtain unpublished reports of ACDA effectiveness.

Included in our effectiveness review were studies with at least 10 patients, studies that evaluated any of the artificial cervical discs on the market, studies that reported on at least one of pain and/or disability outcomes, and studies that reported at least 1 year of outcome data. We excluded non-English language studies, case reports, animal and in vitro studies, duplicate publications, studies that did not examine the outcomes of interest, single-site reports of data included in a multicenter study publication, and studies with greater than 20% loss in study sample at 1-year follow-up.

Quality assessment of studies included in our review of efficacy and effectiveness was conducted by two independent reviewers. Conflicts were solved by consensus. We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system to evaluate the overall quality of the studies included in the review.[10] Internal validity of RCTs was assessed using the Cochrane Musculoskeletal Injuries Group Quality Assessment Tool.[11]

Data were abstracted by two independent reviewers using a data abstraction form designed by our team. We abstracted information on study population, methods, interventions, out-

TABLE 1. Observational Studies and Case Series

Author (yr)	Sample			Artificial Cervical Disc and No. of Levels	Follow-up	Complications	Clinical Outcomes	Conclusions
	Patients	Age (yr)	Sex					
Amit (2007)[12]	22 (22 devices)	Age range: 39–79 Mean age: 51	59.1% male	Bryan (Medtronic, Fridley, Minnesota) 1 level	12 mo	No complications reported.	Significant improvement in VAS, SF-36 mental and physical, and NDI scores at 12 mo's follow-up ($P < 0.001$ for all outcomes mentioned).	Bryan disc arthroplasty achieves neurological decompression, symptom relief, and functional restoration. In addition, movement at the operated level is maintained.
Bertagnoli *et al* (2005)[13]	16 (20 devices)	Age range: 32–60 Mean age: 48.3	50% male	ProDisc-C (Synthesis Spine, West Chester, PA) 1 and 2 levels	12 mo	No complications reported.	Significant improvement of preoperative VAS ($P < 0.05$) and ODI ($P < 0.05$) scores at 12 mo follow-up. Significant change in ROM from 3 wk to 12 mo follow-up ($P < 0.001$).	ProDisc-C arthroplasty provides significant improvement in pain and functional outcome scores and did not result in any spontaneous fusions at the level of the surgery or at adjacent levels.
Duggal *et al* (2004)[14]	26 (30 devices)	Age range: 30–67 Mean age: 3.3 ± 7.93	61% male	Bryan 1 and 2 levels	24 mo	Increased postoperatory radicular pain (1 case). Transient unilateral vocal cord paralysis (1 case). Dysphagia (1 case). Device migration (1 case).	A statistically significant improvement in the mean NDI scores was seen between preoperative and late-postoperative scores ($P < 0.05$).	Insertion of the Bryan Cervical Discprosthesis following anterior cervical discectomy appears to be safe and provides good preliminary clinical results.
Goffin *et al* (2003)[15]	103 single-level 43 bilevel	Age range: 26–79 (single-level) 28–62 bilevel	40.8% male (single-level) 58.1% male (bilevel)	Bryan 1 and 2 levels	24 mo	Prevertebral hematoma (2) Residual myelopathy (1) Unresolved pain (2) Disc herniation (1) Temporary dysphonia (1) CSF leak (1)	86% of single-level patients and 96% of bilevel patients were assessed as excellent, good, or fair on Odom's classification at 12 mo follow-up.	Discectomy and implantation of the Bryan cervical disc prosthesis alleviates symptoms, supports maintenance of motion, and is safe with a quick recovery.

(*Continued*)

TABLE 1. (*Continued*)

Lafuente *et al* (2005)[17]	46 (46 devices)	Age range: 33–70 Mean age: 47.6	60.9% male	Bryan 1 level	12 mo	Worsening of muscle spasm (1). Dysphopnia (3) Prosthesis removed and replaced with interbody cage (1).	Significant improvement in VAS ($P <$ 0.0001), SF-36 mental ($P <$ 0.0001) and physical ($P < 0.0001$), and NDI ($P < 0.0001$) scores at 12 mo follow-up.	The Bryan cervical disc replacement was shown to be reliable and safe for the treatment of patients with cervical spondylosis, producing minimal complications and good surgical results.
Mehren *et al* (2006)[18]	54 (77 devices)	NS	NS	ProDisc-C 1 and 2 levels	12 mo	HO that led to restrictions of the ROM (8). Spontaneous fusion (7). There was a statistically significant higher rate of HO in multilevel versus single-level cases.	Significant improvement in VAS ($P <$ 0.0001) and NDI ($P<0.0001$) scores at 12 mo follow-up.	The high rate of spontaneous fusion 1 yr postsurgery impacts on the expectation of movement preservation after ACDA.
Pimenta *et al* (2004)[19]	53 (82 devices)	Age range: 26–68	39.6% male	PCM (Waldemar, Hamburg, Germany) 1, 2, 3, and 4 levels.	1 yr	Anterior displacement of prosthesis (1). McAfee Grade 1 HO (1).	57% of the patients had excellent and 40% good clinical results according to Odom's criteria at 1 yr follow-up.	The PCM arthroplasty appears to be less invasive than fusion and allows reconstruction of more unstable conditions than previously reported with disc replacement.
Pimenta *et al* (2007)[20]	140 (229 devices)	Age range: 28–77 (single-level) 28–80 multi-level	39.4% male (single-level) 40.6% male (multi-level)	PCM 1, 2, 3, and 4 levels	3 yr	HO (1) Reintervention (5)	The NDI ($P < 0.021$), VAS, TIGT, and Odom's criteria scores improvement was better for multiple-level than single-level patients.	This study helped define the category of patients who could be most helped by ACDA.
Robertson (2004)[21]	17	Age range: 32–75 Mean age: 50	58.8% male	Prestige I (Synthesis Spine: West Chester, PA) Disc NS	4 yr	None reported	The NDI, VAS arm pain and neck pain, and SF-36 PCS, MCS, and EMS scores improved at the 4th yr follow-up (% improvement were 30.5, 55.9, 42.9, 11.5, 13.4 and 2.8, respectively)	The improvement in clinical out comes maintained after 4 yr.
Sahoo (2006)[22]	20	Age range: 31–50	70% male	Bryan 1 level	24 mo	Temporary hoarseness of voice (1).	At 24 mo follow-up, 80% rated excellent and 20% rated good according to Odom's criteria.	Implantation of the Bryan disc resulted in excellent or good outcomes in all patients.

(*Continued*)

comes, and complications. Clinical studies evaluating the efficacy and effectiveness of ACDA, either alone or in comparison to cervical fusion, were analyzed qualitatively. When needed as an information source, primary authors and manufacturers were contacted to obtain unreported data from the articles reviewed.

The clinical outcomes of interest were 36-Short Form Health Survey (SF-36) scores, neck and arm pain scores, and neck disability index (NDI) scores. These clinical scales are widely used to evaluate the overall function and quality of life (SF-36) and cervical spine function in patients undergoing surgery for cervical DDD.

RESULTS

The literature search yielded 622 titles. After the title and abstract review, we excluded 175 studies of surgical treatment of cervical DDD other than ACDA (fusion, laminoplasty, *etc.*); 33 records of *in vitro*, animal, or cadaveric studies of artificial cervical discs; eight case reports; nine studies published in other language than English; and 264 records of editorials, comments, anatomic studies, and studies of diseases other than cervical DDD. After a full-text review of the remaining records, we excluded 91 studies that did not report any clinical data on ACDA, 11 case series with less than 12 months of follow-up, six case-series with greater than 20% of the sample loss to 1-year follow-up, and one single-site report of an RCT (multisite data that may have included the single-site were reported in another study). Three studies that included data reported in a previous published study were excluded.

We included in our review 13 case series presenting clinical data on the effectiveness of ACDA (single and multiple-level ACDA) and three RCT reports of effectiveness of single-level ACDA compared to single-level fusion. One accepted RCT report received from the authors and one nonrandomized comparative study were also included in our review of effectiveness. The flow of this systematic review is presented in Figure 1.

Thirteen case series met our criteria and were included in our review of effectiveness. The data abstracted from these studies are summarized in Table 1. These studies provide low GRADE of evidence (further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate).[26] Below, we present the main findings of these studies, grouped by the number of levels at which ACDA was performed (single-level, one or two-level, and up to four-level ACDA).

Single-Level ACDA

Three case series included patients with one-level ACDA.[12,17,22] The ACDA was performed using the Bryan cervical disc. The authors reported significant improvement in clinical outcomes at 12 month's and 24 month's follow-up.

One- or Two-Level ACDA

Seven case series included patients with one- or two-level ACDA. In five studies, the authors used the Bryan cervical disc,[14–16,24,25] while two studies reported observational data on Pro-Disc C.[13,18] All seven studies reported significant improvement in clinical outcomes at 12 and 24 months. One of

TABLE 1. (*Continued*)

Wang *et al* (2006)[24]	83 (102 devices)	Age range: 34–58 Mean age: 49	52% male	Bryan 1 and 2 levels	24 mo	Esophageal injury (1). Spontaneous fusion (1). Worsening of preoperatory cervical kyphosis (2).	73% and 27% of patients reported excellent and good outcomes, respectively according to Odom's criteria.	Bryan cervical disc prosthesis partially restored flexion–extension and lateral bending in the impaired segment while maintaining the advantage of anterior decompression.
Yang *et al* (2008)[25]	19 (23 devices)	Age range: 35–52 Mean age: 42.5	63% male	Bryan 1 and 2 levels	24 mo (average)	Position deflexion of the prosthesis metal endplates (4 levels).	68% and 32% of patients reported excellent and good outcomes, respectively according to Odom's criteria. The mean JOA scores significantly improved at the final follow-up examination ($P < 0.05$)	ACDA appeared to be safe and provided encouraging clinical and radiological outcomes.

HO, heterotopic ossifications; JOA, Japanese Orthopedic Association; NDI, neck disability index; ODI, The Oswestry Disability Index; ROM, range of motion; SF-36, short form health survey; TIGT, treatment intensity gradient test; VAS ∇ visual analogue scale (pain intensity).

TABLE 2. Randomized Controlled Trials

Author (yr)	Sample						Artificial Cervical Disc and No. of levels	Follow-up	Complications	Clinical Outcomes	Conclusions
	ACDA			Fusion							
	Number	Age (yr)	Sex	Number	Age (yr)	Sex					
Mummaneni *et al.* (2007)[6]	276	Mean age: 43	46% male	265	Mean age: 44	46% male	Prestige ST 1 level	24 mo	*Reinterventions* ACDA: hardware removal (5). Fusion: additional revisions (5), supplemental fixation (9), hardware removal (9). *Adverse events* ACDA: numbness/paresthesia (back, leg, and arm), sleep apnea, bursitis, screw fixation, dysphagia, low-bone density, Lhermitte phenomenon, hematoma, cervical radibulopathy, dysphonia, spinal fluid leak, UTI, headaches, intrascapular muscular spasm, sinusitis (17). Fusion: venous bleeding, arm numbness, headaches, nausea, cerebrospinal fluid leak, dysphagya, headaches, vomiting, dysphonia, spinal fluid leak (11).	Significantly greater improvement in neck pain in the ACDA group at 12 mo ($P < 0.035$). Significantly higher success rate (neurological status) in the ACDA group at 12 and 24 mo ($P < 0.006$ and $P < 0.005$, respectively). The ACDA group patients return to work faster (45 days) than the fusion group patients (61 days). Prescription: the ROM was maintained in ACDA patients, while it was restricted in fusion patients.	The Prestige ST disc replacement maintains physiological segmental motion and is as safe and effective as fusion for the treatment of cervical DDD.
Murrey *et al.* (2009)[27]	103	Mean age: 42.1	44.7% male	106	Mean age: 43.5	46.2% male	ProDisc-C 1 level	24 mo	Three ACDA patients did not achieve AE success (the absence of adverse events) because of two implant-related and one implantation events. Seven fusion patients did not achieve AE success because of neck pain/pseudoarthrosis requiring revision, allograft, and plate subsidence requiring revision, dysphagia, chronic pain, cervical myofascial dysfunction, and dysphagya associated with plate migration requiring revision; postoperative wound infection at the anterior cervical wound characterized as a SLTAE, and revision of fusion because of SLTAE neck pain.	At 24 mo, the neurological success rate and the NDI success (≥15 point improvement) were higher in the ACDA group compared to the fusion group, but the difference was not statistically significant. Prescription: in ACDA patients, ROM was 8.4° preoperative and 9.4° at 24 mo; in fusion patients, ROM was 7.7° preoperative and 0.9° at 24 mo.	ProDisc-C total disc replacement is viable surgical option for patients with symptomatic cervical disease and may have both short- and long-term benefits compared to the current standard of care.

(*Continued*)

TABLE 2. (*Continued*)

Nabhan *et al.* (2007)[28]	19	NS	NS	21	NS	NS	ProDisc-C 1 level	1 yr	Nine patients in the fusion group and two patients in the ACDA group required a secondary surgical procedure (revision, removal, or reoperation of the implant or supplemental fixation) Subarachnoid hemorrhage in the ACDA group (1)	Prescription: the ROM decreased in both groups; there was a significant higher decrease in the fusion patients ($P < 0.001$).	Cervical spine prosthesis can maintain segmental micromotion within 1 yr after surgery. The procedure has comparable clinical results to that of fusion.
Sasso *et al.* (2007)[29]	56	Mean age: 42	53.6% male	59	Mean age: 46.1	54.2%	Bryan 1 level	24 mo	*Reinterventions* ACDA: fusion for adjacent level disease (3) Fusion: posterior cervical fusion for symptomatic nonunion (1), revision of fusion for nonunion (1), fusion for adjacent level disease (2).	NDI and VAS neck pain scores decreased significantly more at 24 mo in the ACDA group ($P < 0.006$ and $P < 0.014$, respectively). No difference between groups in VAS arm pain scores decrease.	Cervical arthroplasty with Bryan cervical disc compares favorably with fusion.

**WHO adverse events grades: grade 1 ∇ mild; grade 2 ∇ moderate, grade 3 ∇ severe, grade 4 ∇ life threatening or disabling, grade 5 ∇ fatal*

NDI, neck disability index; ROM, range of motion; SF-36, ∇ short form health survey; SLTAE, sever or life-threatening adverse event; VAS, visual analogue scale (pain intensity).

the studies, involving the ProDisc-C, reported a high rate of spontaneous fusion (50%) at 12 month's postsurgery.[18]

Up to Four-Level ACDA

Two case-series report data on patients with up to four-level ACDA, using the PCM cervical disc. One study[19] reported significant improvement in clinical outcomes at 12 month's follow-up. A subsequent publication by the same authors[20] reported that the improvement in clinical outcomes at 3 years of follow-up was more significant in patients with multiple-level than single-level arthroplasty. One study reports data on up to three-level ACDA patients using the Bryan cervical disc.[23] The authors noted a significant improvement in pain scores at 12 months of follow-up in patients who had already undergone cervical fusion or posterior foraminotomy.

Randomized Controlled Trials

We found four RCTs comparing clinical outcomes of single-level ACDA to single-level fusion (one unpublished report). Data abstracted from these reports is presented in Table 2. One nonrandomized comparative study was also included in our review (Table 3). When methodologically sound, RCTs provide high GRADE level of evidence (further research is very unlikely to change our confidence in the estimate of effect)[26] on the single-level ACDA compared to single-level cervical fusion.

The summary of the methodological quality assessment of the RCTs included in our report using the Cochrane Musculoskeletal Group Methodological Assessment Tool[11] is presented in Table 4. Most of these RCT reports failed to mention if the analysis was intention-to-treat, blinding of assessors, and blinding of patients. However, because of the use of different devices and surgical procedures for each type of treatment compared in these RCTs, we acknowledge that it is impossible to blind the treatment provider.

Mummaneni et al.[6]

This is a report of an federal drug administration (FDA)-regulated investigational device exemption (IDE) study that evaluates the safety and effectiveness of the PRESTIGE ST cervical disc system. The study is ongoing and this article reports an interim analysis of 250 patients at 2 years of follow-up. The authors conclude that the Prestige ST disc replacement maintains physiological segmental motion and is as safe and effective as fusion for the treatment of cervical DDD. Although the results are encouraging, the collection of information is not complete. In addition, the presentation of the results (only mean scores are presented without standard deviation) precludes estimation of effects that can be used in a meta-analysis with any degree of confidence.

Murrey et al.[27]

This article reports the results of an FDA-regulated IDE study evaluating the safety and effectiveness of the ProDisc-C compared to fusion. The clinical outcomes and adverse events were reported for 209 patients, with up to 2 years of follow-up. The authors concluded that the ProDisc-C total disc replacement is a viable surgical option for patients with symptomatic cervical disease and may have

TABLE 3. Comparative, Nonrandomized Trial

Author, (yr)	Sample						Artificial Cervical Disc and No. of Levels	Follow-up	Complications	Clinical Outcomes	Conclusions
	ACDA			Fusion							
	Number	Age (yr)	Sex	Number	Age (yr)	Sex					
Wigfield *et al.* (2002)[30]	12	Mean age: 49	75% male	13	Mean age: 57.8	77% male	NS 1 level	12 mo	Not reported	Comparison of the NDI scores showed a statistically significant improvement in the ACDA group but nothing in the fusion group.	The ACDA may be reserved for use in patients with advanced disease and previous fusions, with the primary goal of preserving motion the operative site. Alternatively, ACDA may prevent cervical spondylosis.

both short- and long-term benefits compared to the current standard of care.

The results are reported as percentage of patients experiencing overall success (defined as NDI success, neurological success, device success, and absence of adverse events related to the implant or its implantation) at 24 months. The trial was initially conceived and powered as a noninferiority trial using a dichotomized composite endpoint. The noninferiority margin was 10%. Nevertheless, the manuscript generally reports tests of superiority. At some points in time and on some measures, the outcomes for the ProDisc-C patients are superior to the outcomes for the fusion patients, but this is not consistent. Plots with distributions of scores are presented in this article, but the standard deviations of these scores are not clear. Although plots contain error bars, it is not clear if they represent confidence intervals, standard deviation, or even standard error. In studies such as this reporting of change scores and variability of change, scores can help provide more meaningful comparisons.

***Nabhan et al.*[28]**

This is an RCT testing effectiveness of ProDisc-C compared to fusion in 49 patients with radiculopathy after 1 year of follow-up. The authors concluded that the cervical disc replacement can maintain segmental motion within 1 year after surgery and that the clinical results of ACDA and fusion are similar. Data reported include means and standard deviations of clinical outcomes assessed at each point in time for each group. Statistical significance of change in clinical outcomes between baseline and the follow-up was calculated for each treatment group allowing us to calculate the statistical significance of the mean differences between the control and the intervention groups ($\hat{\mu}C–\hat{\mu}I$) (Table 5).

These results provide statistical evidence that the change in neck pain and arm pain scores were larger in the ACDA group than in the fusion group ($P < 0.05$), suggesting ACDA has better clinical outcomes than fusion, at 1 year of follow-up. Nevertheless, the baseline neck pain and arm pain scores were not taken into account (because of lack of adequate information reported), which might affect the significance of the difference in change from baseline between the two groups.

***Sasso et al.*[29]**

This is a report from three sites of a multicenter FDA IDE trial for the Bryan Cervical Disc. One hundred and fifteen patients were enrolled in the trial (56 patients in the ACDA arm and 59 in the fusion arm) and followed prospectively for 2 years. The authors concluded that cervical arthroplasty with Bryan cervical disc compares favorably with fusion.

At 1 year, only six patients were lost to follow-up (5%). The loss to follow-up increased dramatically at 24 months (71 patients in total at 24 months, 61%). This has the potential to introduce "selection bias," and there is evidence of selection bias in the tables reported. In the absence of selection bias, the effects observed at a given point in time would be expected to be the same as a comparison of changes at 24 months. In the presence of selection bias, the "difference of differences" approach to the analysis would be preferable as it would address

TABLE 4. Summary of the Methodological Quality Assessment of the RCT Reports (Cochrane Musculoskeletal Injuries Group)

	Mummaneni *et al* 2007[6]	Murrey *et al* 2009[27]	Nabhan *et al* 2007[28]	Sasso *et al* 2007[29]
Concealment	2	2	2	2
ITT analysis	0	0	1	0
Blinding of assessors	0	0	0	0
Baseline	2	2	0	2
Blinding of patients	0	0	2	0
Blinding of treatment provider	0	0	0	0
Care programs	2	2	0	2
Inclusionexclusion criteria	2	2	2	2
Intervention	2	2	2	2
Outcomes	2	2	2	2
Diagnostic test	2	2	2	2
Follow-up	2	2	2	2
TOTAL	**16**	**16**	**15**	**16**

Cochrane Musculoskeletal Injuries Group Methodological Assessment Tool includes aspects of internal and external validity of RCTs. Individual scores for each item are assigned (2, 1, or 0), and a total score is optional and may be obtained by summing the scores of individual items. The scores for the last three items used in the total score are those for the primary measure of the systematic review. In cases where the items remain unknown, all items are designated the lowest score except for allocation concealment where the middle score is given. The higher the total score, the higher quality of the RCT is. The maximum possible total score is 24.

differences in baseline characteristics. In their article, Sasso *et al* test differences at different points in time without adjusting or accounting for differences in scores at baseline. However, they provide enough information to calculate the means differences between the control and the intervention groups at 24 months. We calculated the mean differences for all the clinical outcomes reported by the authors. The appropriate estimates of effect for this study are presented in Table 6. From this table, it is evident that although there is statistical evidence for differences between groups at 24 months that favors the Bryan disc, there is no longer statistical evidence for these effects, when tests account for the baseline scores.

We contacted the corresponding authors of all the articles that did not provide sufficient data to be included in a meta-analysis. We failed to obtain any unpublished data from the authors we contacted using the e-mail addresses provided in the articles.

Nonrandomized Comparative Study

Nonrandomized comparative studies provide moderate GRADE level of evidence (further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate).[26] We found one such study to consider.

Wigfield et al.[30]

The authors conducted a prospective, nonrandomized study of 25 patients (12 in the ACDA group, 13 in the fusion group) with single-level cervical DDD. A comparison of the NDI scores showed a statistically significant improvement in the ACDA group. The improvement in the fusion group was not statistically significant. This study reported that adjacent-level movement increased in the fusion patients compared to ACDA patients at 12 months of follow-up. Nevertheless, the results of this study do not clarify whether ACDA has a protective influence on adjacent intervertebral discs.

Conclusions from this study should be considered with caution. The authors did not adjust for the baseline NDI scores, which were higher in the ACDA group. Moreover, the selection of patients in a nonrandomized fashion may introduce selection bias and affect the generalizability of the results.

DISCUSSION

This is the first descriptive systematic review that identified the best available evidence to document the effectiveness of ACDA.

The case series reviewed in this report suggest that most clinical outcomes of ACDA are comparable to those of fusion—the standard procedure for DDD patients referred for surgery. Also, several randomized controlled trials found no statistical evidence of differences between ACDA and fusion in terms of effectiveness and safety. The main difference in the outcome

TABLE 5. Statistical Significance of the Mean Differences ($\hat{\mu}C - \hat{\mu}I$) Reported by Nabhan *et al* 2007[28]

Clinical Outcome		*P*
Neck pain	2.00 $\hat{u}_C$–$\hat{u}_I$	0.042
Arm pain	2.00	0.02

TABLE 6. The Mean Differences for All the Clinical Outcomes Reported by Sasso *et al* 2007[29]

	12 Months		24 Months		24 Months (Adjusted)	
Clinical Outcome	Means Difference	*P*	Means Difference	*P*	Means Difference	*P*
SF-36 physical score	−4.10	0.0349	−5.90	0.0164	−3.40	0.167
SF-36 mental score	−1.80	0.282	−5.90	0.0164	−4.70	0.084
Neck disability index	7.90	0.012	11.5	0.006	5.20	0.217
Neck pain	9.80	0.057	17.10	0.013	11.8	0.111
Arm pain	10.30	0.036	10.10	0.150	6.00	0.438

of ACDA compared to fusion is preservation of spine mobility. However, at this time, there is no evidence to support the hypothesis that preservation of segmental mobility with disc arthroplasty provides better long-term outcome than fusion by limiting the adjacent-level DDD. It is likely that longer follow-up periods will be necessary to properly test this hypothesis.

There are several limitations to our review. First, we included only studies published in English, which is a possible source of selection bias. Second, the follow-up period of most of the studies included in our review of effectiveness is limited to 2 years (24 months), which precludes any conclusions on the long-term effectiveness and safety of the ACDA procedure. Third, despite the fact that preliminary results of ongoing RCTs comparing single-level ACDA to single-level cervical fusion have been published, we were unable to perform a meta-analysis because of methodological and reporting deficiencies. None of the reported trials appeared to follow the established guidelines for RCT reporting, and there was a lack of consistency across trials in the methods of presenting the information. Our attempt to contact the authors in order to obtain unpublished data was met with failure.

ACDA is a surgical procedure that may replace cervical fusion in selected patients suffering from cervical DDD. In most instances, within 2 years of follow-up, the effectiveness of ACDA appears similar to that of cervical fusion (moderate to strong GRADE evidence). Weak evidence exists that ACDA may be superior to fusion for treating neck and arm pain. Future studies should report change scores and change score variance in accordance with RCT guidelines in order to strengthen credibility of conclusions and to facilitate meta-analyses of studies.

Key Points

- Artificial cervical disc arthroplasty is a surgical procedure that may replace cervical fusion in selected patients suffering from cervical degenerative disc disease.
- Artificial cervical disc arthroplasty appears to be at least as effective as cervical fusion in the short term (up to 2 years of follow-up).
- Further RCTs should adhere to reporting guidelines in order to strengthen credibility of conclusions and to facilitate meta-analyses of studies.

Acknowledgments

Production of this document has been made possible by a financial contribution from Alberta Health and Wellness and under the auspices of the Alberta Health Technologies Decision Process initiative: the Alberta Model for health technology assessment and policy analysis. The views expressed herein do not necessarily represent the official policy of Alberta Health Services. The authors would like to thank Dr. R. John Hurlbert for his perspective and advice during this review process.

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