Iatrogenic Contributions to Cervical Adjacent Segment Pathology

Review Article

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Abstract *Background:* Anterior cervical discectomy and fusion (ACDF) is widely accepted as a predictably excellent procedure. On the other hand, adjacent level pathology following ACDF is a well-known phenomenon which undercuts surgical outcome. However, the extent to which ACDF accelerates this phenomenon in the naturally degenerating cervical spine is still to be understood. *Questions/Purposes:* To summarize the current evidence concerning adjacent segment pathology in the light of biomechanics, natural history, postoperative course, and comparison between ACDF and total disc replacement (TDR). *Methods:* This is a study of published articles. Articles were searched by the topic of adjacent disc pathology in cervical spine through Google Scholar and Pubmed. After review, 37 published articles were deemed suitable for the subject of this study. *Results:* Biomechanical and clinical data strongly suggest that ASP is a presentation of the iatrogenically accelerated natural aging process of cervical spine. However, power study analysis with assumption showed that current RCTs are unlikely to prove this suggestion. *Conclusion:* Available data suggests that iatrogenic factors play a significant role in adjacent segment pathology following ACDF.

Keywords adjacent segment pathology · anterior cervical discectomy and fusion · total disc arthroplasty · prognosis · reoperation

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Introduction

Since first reported by Smith and Robinson, anterior cervical discectomy and fusion (ACDF) has become a widely accepted surgical procedure which can address a wide range of cervical spinal disorders and provide excellent outcomes in well-selected patients [29, 32, 33]. However, many spine specialists believe that the alteration of spinal biomechanics induced by fusion lead to radiographically and clinically evident degenerative changes at adjacent levels.

Degenerative changes in the cervical spine are accepted to be a part of the natural aging process, but these changes are generally accepted to be accelerated postoperatively following ACDF. The precise extent to which ACDF accelerates this natural degenerative process is a matter of controversy in the spine surgery community. The purpose of this paper is to summarize current evidence regarding adjacent segment pathology, from the view points of biomechanics, natural history of the cervical spine, postoperative course after ACDF, and comparison between ACDF and total disc replacement (TDR) (Fig. 1).

Method

This is a study of published articles. Articles were searched by the topic of adjacent disc pathology in cervical spine through Google Scholar and Pubmed. After review 37 published articles were deemed suitable for the subject of this study.

Results

Terminology

Recently, a consensus panel of spine surgeons proposed the term “Adjacent segment pathology (ASP)” to describe changes that occur adjacent to a previously fused level [3]. The subcategories of radiographic ASP (RASP) and clinical ASP (CASP) were also defined recently to consolidate the

Fig. 1. A case example of C5/6 total disc replacement. Preoperative (above) and 18-month postoperative (below) flexion-extension X-rays are shown. Index level remains mobile 18 month postoperatively (below).

multitude of terms that historically have been used to describe this phenomenon. RASP refers to radiological changes that occur at the adjacent segment, whereas CASP refers to clinical symptoms and signs that occur at the adjacent segment. The terms ASP, RASP, and CASP are used in this article to express the above-mentioned phenomena.

ACDF represents cervical interbody fusion surgery with or without plate fixation devices, while TDR indicates the replacement surgery of intervertebral discs with anterior artificial motion-sparing device with aiming at restoring biomechanical function of natural discs.

Natural History

The human spine degenerates as a part of the natural aging process, and in the course of time, symptoms may also arise [35]. The fact that degenerative changes occur naturally over time makes it difficult to know if adjacent level degenerative changes seen after fusions result from the natural history of the degenerative process or are secondary to the fusion itself. The incidence of age-related degeneration of the cervical spine resulting in clinical symptoms over time has been studied. Gore found in his long-term follow-up study of 159 asymptomatic individuals across a wide age range that 24 (15%) developed neck pain, and 1 required surgical treatment for radiculopathy over a 10-year follow-up period [12]. Matsumoto followed 201 asymptomatic healthy volunteers for more than 10 years (11.7 years on average) with cervical MRI and reported 9% developed neck pain, 7% developed headache, 28% complained of shoulder stiffness,

and 5% had numbness in the upper extremities at final follow-up [24].

Radiographic changes as a result of natural aging have also been reported. Gore also found in his 10-year follow-up study that of 87 people who did not have radiographic degenerative changes in the cervical spine at entry, 30 developed de novo degenerative changes (34.4% after 10 years), and 107 out of 159 people (67.3%) had some progression of degenerative changes [12]. Wilder followed 707 people radiographically over 5.8 years on average, and reported 339 (47.9%) had progressive radiographic cervical spine degeneration [35]. He also found that progression of cervical disc degeneration was more common progressed in females between the ages of 40 and 60 years, and in males between the ages of 60 and 79 years.

Matsumoto also clarified that radiographic (MRI) degenerative changes did not always result in clinical symptoms [24]. Among those who had degenerative findings in their MRI, approximately 20 to 50% of people had neck pain, 10 to 30% had headache, 50 to 80% had shoulder stiffness, and 30 to 50% had upper extremity numbness. This discrepancy between radiographic degeneration and clinical symptoms was also noted by Carrier in his review on ASP [7]. He found that the incidence of RASP after 1–2 levels of ACDF was 27.3%, and after 3–5 levels was 29.7%, while CASP was only 11.9% in total. The gap between the incidences of RASP and CASP reflects the discrepancy between radiographic findings and clinical presentation. Although it is still unknown whether radiographic degeneration can be a precursor to symptomatic spondylosis, the existence of this gap must be borne in mind when RASP and CASP are discussed. Furthermore, the progressive radiographic and symptomatic cervical degenerative changes that are known to occur as a part of natural aging make it difficult to understand the role of fusion on the development of ASP.

Biomechanical Studies

The vast majority of biomechanical studies have demonstrated that cervical fusion causes potentially deleterious secondary effects in adjacent levels. In a human cadaver study of ACDF, Eck showed that intradiscal pressures at adjacent levels increased significantly, and that the range of motion (ROM) at both cranial and caudal adjacent levels increased although not statistically significant [10]. Dmitriev measured intradiscal pressures in flexion/extension and ROM at adjacent levels in intact, TDR, and ACDF models in human cadavers, and found both intradiscal pressure and ROM at adjacent levels increased in the ACDF model, whereas the TDR model did not induce significant adjacent level changes [9].

Increased ROM at adjacent levels after ACDF has also been reported in human radiographic studies as discussed later, and this supraphysiologic motion, possibly arising to compensate for motion lost at fused levels, is thought to be one reason why RASP is accelerated after ACDF. Furthermore, altered intradiscal pressures at adjacent levels after ACDF could also lead to acceleration of disc degeneration. Disc nutrition and intradiscal perfusion are dependent on

diffusion and osmotic pressure gradients [15]. Chronically elevated disc pressures could negatively affect disc nutrition, disturbing homeostasis of the disc structure resulting in accelerated intervertebral disc degeneration.

Follow-Up Studies After ACDF

RASP in ACDF

Multiple studies have documented elevated rates of RASP following ACDF compared to control groups. Gore followed an ACDF group and a control group over 5 years and found that the ACDF group developed adjacent level anterior osteophytes more frequently compared to the control group [12, 14].

Baba followed 106 cases after ACDF over 8.8 years and found that ROM at adjacent levels increased both cranially and caudally, and that this increased ROM was a precursor to spondylosis [5]. These clinical findings mirror those of cadaveric biomechanical studies [9]. Increased intradiscal pressures at adjacent levels can also be reasonably assumed in vivo settings which would also be reasonably expected to accelerate ASP after ACDF.

Goffin followed 180 patients for greater than 60 months who had required ACDF for various pathologies including trauma, degenerative spondylosis, and infection/tumor [11]. Postoperative progression of degenerative radiographic changes was statistically similar among trauma cases, radiculopathic cases, and myelopathic cases. This similarity in progression of degeneration at adjacent levels between younger trauma cases without preexisting degenerative disc disease or excessive genetic predisposition to cervical degeneration and older nontraumatic degenerative spondylotic cases may suggest that not only natural progression of preexisting degenerative disc disease but also biomechanical factors due to ACDF play important role in adjacent degeneration after ACDF.

CASP in ACDF

Multiple studies of CASP suggest that ACDF results in increased incidence of CASP compared to non-operated control groups. Matsumoto found more frequent degenerative changes in adjacent disc spaces in ACDF patients compared to control groups [24]. At follow-up after a 12-year interval on average, ACDF patients had more neck pain and shoulder stiffness, and people with lower disc height and foraminal stenosis at adjacent levels had more neck pain and shoulder stiffness, although not all the radiographic findings were accompanied by clinical symptoms as previously mentioned. These data suggest that accelerated RASP after ACDF correlate with the development of CASP.

Several authors have reported on the incidence of revision surgery after ACDF for symptoms attributable to adjacent level degeneration [13, 17, 19, 35] (Table 1). Reported incidence rates are 6 to 17% over various follow-up periods, and are estimated at 1.5–3.8%/year. In contrast, Gore reported that only one of 159 (1%) asymptomatic people required surgery over 10 years [12]. Although direct comparison of retrospective studies has limited methodological value, the

Table 1 Incidence of revision surgery after ACDF for symptomatic adjacent level degeneration

	Number	Revision %	f/u year	%/year
Yue	71	17	7.2	2.4
Bohlman	122	9	6	1.5
Gore	146	14	5	2.8
Williams	60	17	4.5	3.8
Ishihara	112	6	2	3.0

f/u follow up, yr year

influence of fusion on the accelerated development of symptomatic adjacent degeneration cannot be denied.

ACDF in Comparison with TDR

Radiographic Analysis Insight into the natural history of ASP can be gained by analysis of the ACDF control group from the TDR investigational device exemption (IDE) studies. Kelly compared 100 TDR and 99 ACDF cases from the IDE studies radiographically after 2 years of follow-up and found no statistical difference in ROM at adjacent level between two groups [21]. On the contrary, Auerbach reported differently [4]. He followed 93 TDRs and 94 ACDFs over 2 years radiographically, and found that C2C7 ROM increased by 5.9° after TDR but decreased by 0.8° after ACDF, and that the ROM at each mobile segment increased by 1 to 6% after ACDF to compensate the lost ROM at the fused level.

Maldonado analyzed RASP in TDR and ACDF groups after 36 months of follow-up, and reported 8.8% after TDR and 10.5% after ACDF, which didn't reach statistically significant difference [23].

CASP and Reoperation Rate

Robertson compared TDR group (74 cases) and ACDF (158 cases) group after 2 years of follow up [28]. Symptomatic DDD was 1.3 vs. 13.9%, CASP was 0 vs. 11 (7%), and reoperation was for CASP was 0 vs. 2 in TDR group and in ACDF group, respectively. Medical treatment for neck, shoulder, and arm pain was used in 1.3% in TDR group vs. in 33% in ACDF group.

Jawahar followed 39 TDRs and 25 ACDFs for 36 months on average and found CASP 15% in TDR group and 18% in ACDF groups [20]. He didn't find statistical difference between these two groups ($p=0.085$), but found that concurrent lumbar disc degeneration is the risk of symptomatic adjacent level pathology.

Some authors report reoperation rate at adjacent level for CASP ($n=99$ –1,229, follow up <5 years) [1, 2, 6, 8, 25, 28, 31, 30] (Table 2). The reoperation rate over various range of follow-up duration was 0.6–5.5% in TDR group and 2.2 to 13.1% in ACDF group, and 0.7–1.4%/year in TDR group and 1.6–2.6%/year in ACDF group. Mostly, the difference between the two groups didn't reach statistical significance,

Table 2 Summary of reported reoperation rate in TDR vs. ACDF. In each report, the difference between these two groups did not reach statistical significance, but in all studies, the reoperation rate and the rate per year are higher in ACDF group

Name	Years	<i>n</i> (total)	<i>n</i> (TDR)	Reop TDR	Reop % (TDR)	%/year	<i>n</i> (ACDF)	Reop ACDF	Reop % (ACDF)	%/year
Anderson	2	463	242	7	2.9	1.4	221	9	4.1	2
Anderson	1.5–28 m	1,229	649	4	0.6		580	13	2.2	
Sasso	4	319	181	10	5.5	1.4	138	9	6.5	1.6
Sasso	2	99	49	2	4	2	50	2	4	2
Mumaneni	2	421	223	3	1.3	0.67	198	9	4.5	2.3
Burks	5	271	144	8	5.6	1.1	127	13	10.2	2.0
Robertson	2	232	74	1	1.4	0.68	158	5	3.2	1.6
Delamarter	5	133	72	2	2.8	0.6	61	8	13.1	2.6

reop reoperation, *yr* year

but in all of these studies, the reoperation rate and the rate per year are higher in ACDF group.

Discussion

ACDF is one of the most predictable and effective operations in spinal surgery. In recent years, a growing body of evidence suggests that long-term results may be compromised by the development of ASP. ASP in recent years has been defined by a consensus panel to help consolidate the literature regarding clinical (CASP) and radiographic (RASP) breakdown [3]. However, it is well established that progressive spinal degeneration occurs with time as a part of the natural aging process even in the absence of ACDF [26]. Both biomechanical and clinical studies from various points of view suggest that ACDF influences may accelerate this natural degenerative process at the segments above or below fusion [16, 22, 36]. Careful summary and analysis of the current available evidence of biomechanic, natural history, clinical outcome, and TDR IDE studies may help guide current clinical decision making and future directions for research.

Biomechanical and clinical data strongly suggest that this natural aging process is accelerated iatrogenically by the biomechanical effects of fusion on adjacent levels [27]. Biomechanical studies consistently demonstrate increases in adjacent level intradiscal pressure after fusion which would likely lead to mechanical disc injury and compromised disc nutrition resulting in disturbance of discal homeostasis and acceleration of degenerative changes. Biomechanical study and clinical radiographic studies have demonstrated supraphysiologic motion at adjacent segments, would also be reasonably expected to accelerate the degenerative aging process.

In order to preserve segmental motion and minimize the deleterious biomechanical influence of fusion, and in hopes of decreasing the rate of ASP, TDR was developed. In general, comparable or superior clinical results have been reported for TDR compared to ACDF in randomized controlled studies [2, 25, 28, 31, 30]. Although reoperation rates have been generally higher for ACDF patients than for TDR patients in RCTs, statistically significantly

higher rates of reoperation for CASP have not been found. Power study analysis assuming power of 80% and $\alpha=0.05$ suggests that given the number of available patients, RCTs are unlikely to definitely prove that ACDF leads to accelerated CASP. Assuming rates of CASP of 14% at 5 years and 26% at 10 years [18] and assuming a 50% reduction in the rate of CASP by TDR, 250 and 145 patients per group would be needed to establish a significant difference at 5 and 10-year follow-up, respectively. These numbers of patients are not currently available and are highly unlikely to be available in the future given the size of currently ongoing RCTs and expected loss to follow-up. As such, surgeons will have only biomechanical, in vivo kinematic, and comparative retrospective data to gauge the effect of ACDF on CASP. These data, in our opinion, strongly suggest that ACDF accelerates adjacent level degenerative changes.

As a narrative summary designed to provide an overview and consideration of the relevant data and considerations regarding ASP, this article has related methodological limitations. A summary of currently available evidence in a wide range of studies from biomechanical to clinical research and IDE data are presented. Unfortunately, definitive high-level clinical data to resolve this debate has remained elusive. On the topic of ASP, there is no long-term large scale RCT currently available that allows comparison of ACDF to a nonsurgical group. For the further evidence, larger and longer term prospective randomized research are awaited, however, will likely present an ethical conflict in terms of randomization into surgical and nonsurgical group given the well-established clinical outcome of ACDF, and may not be feasible.

ASP is likely to be multifactorial, and at this point, the contributory role of ACDF remains to be understood. The preponderance of available data suggests that iatrogenic factors play a significant role. It is well accepted that ASP will remain an inevitable complication after ACDF. It is important therefore in clinical settings to anticipate ASP after ACDF, and to take this into consideration when planning surgical treatment of cervical pathology.

Disclosures

Conflict of Interest: Haruki Ueda, MD, Russel C. Huang, MD, and Darren R. Lebl, MD have declared that they have no conflict of interest

Human/Animal Rights: This article does not contain any studies with human or animal subjects performed by the any of the authors.

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