Adjacent-Level Disease: Fact and Fiction

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Keywords

Adjacent disease · Arthroplasty · Cervical fusion · Disc replacement · Motion preservation

Introduction

The topics of adjacent segment (AS) degeneration and disease have been increasingly discussed with the development and adoption of motion preserving devices. AS degeneration is defined as new degenerative radiographic changes at a spinal level immediately above or below surgically treated levels. When this degeneration is associated with clinical symptoms, including radiculopathy, myelopathy, or mechanical instability, then the appropriate terminology is AS disease. Controversy exists as to whether AS disease is primarily due to the natural progression of an underlying degenerative process or an accelerated process due to increased forces placed on adjacent segments following fusion surgery. In theory, motion preserving devices would eliminate or significantly decrease any accelerated degeneration related to fusion and increased biomechanical stress. Both clinical and laboratory studies have addressed

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AS degeneration and disease as well as the factors leading to their development. In this chapter, we will review these studies as well as examine the evidence basis regarding the effect of motion preservation technology on the incidence of AS disease.

Historical Perspective

The etiology of AS disease has been controversial with some studies suggesting that fusion places significantly increased stress on adjacent segments while others arguing that AS disease is primarily due to the natural progression of underlying disease. Furthermore, there is debate over whether motion preservation devices with their ability to eliminate increased forces on the adjacent discs can decrease AS disease.

Historically, the annual incidence of AS disease following fusion is generally reported to range from 1.5% to 4.5% (Bohlman et al. 1993; Cauthen et al. 1998; Gore and Sepic 1998; Hilibrand et al. 1999). Hilibrand et al. (1999) reported on 409 total procedures in 374 patients followed for 10 years. In this series, symptomatic AS disease was defined as a combination of new radicular or myelopathy symptoms referable to an adjacent degenerated level on two consecutive office visits based on chart review and surgical records (a nonvalidated outcome measure). The annual incidence was 2.9% per year over the 10-year study period (range, 0.0–4.8% per year). In this frequently cited study, only 27 patients (6.6%) had adjacent level surgery with an annual adjacent level reoperation rate of 0.7%. A similar study by Goffin et al. (2004) evaluated long term outcomes in 180 patients with a mean follow-up of 30.9 months. 92% of patients had radiographic evidence of increased degeneration at long-term follow-up. Interestingly, age and number of levels fused showed no correlation with degeneration (Spearmen $r_s = -0.033$, $P = 0.660$ and Spearman $r_s = -0.011$, $P = 0.879$, respectively), but the length of time after operation was correlated with degeneration (Spearman $r_s = 0.156$, $P = 0.036$). This suggests a multifactorial etiology to AS degeneration given such a high incidence after fusion surgery, but the correlation with length of time after operation suggestive of natural progression.

Though these studies addressed the incidence of AS disease, they did not provide a definitive etiology. Biomechanical studies by Eck et al. (2002) were performed to evaluate the intradiscal pressure after cervical fusion. In cadaveric specimens, the authors found that increased intradiscal pressure resulted with normal range of motion after fusion. Increased segmental motion adjacent to fusion segment resulted in increased pressures. They were unable to make conclusions regarding increased intradiscal pressure and effect on normal degenerative changes. Additional biomechanical studies using a finite element model of the cervical spine by Lopez-Espina et al. (2006) showed significant increases in stress of up to 96% on the annulus, nucleus, and endplates of adjacent levels in fused (single and double level) versus normal cervical spines. The authors argued that increased rotation and stress may explain the disc degeneration and osteophyte formation after fusion.

The counter argument for natural progression of spinal degeneration over time is also well supported with radiographic and clinical data. Matsumoto et al. (1998) performed 497 MRI on asymptomatic subjects and found a significant occurrence of degenerative changes and age. In their initial study, 17% of men and 12% of women in their 20s had evidence of degenerative changes compared to 86% of men and 89% of women over 60 years of age. A follow-up of 223 of those patients showed progression of degenerative changes in 81.1% of patients with only 34.1% developing clinical symptoms. These studies suggest a rate of natural progression with age for AS degeneration. Similarly, Gore et al. (2002) followed 159 patients for 10 years with asymptomatic cervical disease. Radiographic degeneration was seen in 72 patients at initial imaging and degeneration progressed in 70 (97.2%) of these patients with15% of patients developing pain over the 10-year study period. These studies identify a clear progression of degeneration over time. In regard to the effect of cervical surgery on the

rate of AS degeneration, Lunsford et al. (1980) reported on 253 patients who underwent anterior cervical discectomy with and without fusion (ACD and ACDF). There was no difference in symptomatic relief and recurrence of symptoms. Further, there was no difference in subsequent development of AS degeneration requiring re-operation.

Motion Preservation Devices

Given the rate of AS degeneration and need for further surgery following fusion, motion preserving devices were developed to theoretically reduce effects of AS disease. Initially developed for the lumbar spine, artificial disc replacement has been performed to prevent loss of vertebral interspace height and reduce pain while maintaining motion. Cadaver studies by Wigfield et al. (2003) showed that artificial disc resulted in reduced stresses in the annulus of neighboring cervical segments compared to simulated fusion. These studies supported the theory that motion preservation resulted in less adjacent segment mechanical stress compared to fusion. The earliest clinical reports of disc replacement in the cervical spine were reported by Fernstrom in 1966. His device was used in a series of 32 patients with 74 cervical disc prosthesis reported by Reitz and Joubert (1964) with good results in all patients and preservation of mobility. The earliest reports of AS degeneration after artificial disc replacement were reported by Cummins et al. (1988). In 18 patients with 5-year follow-up, there was no reported adjacent joint degeneration and motion was preserved on flexion and extension x-ray films.

Motion Preservation Effect

Early US Investigational Device Exemption (IDE) trials of artificial disc replacement showed that results were equivalent in regard to neurologic outcome and surgical success, but data regarding AS degeneration was more difficult to assess given the short follow-up. Heller et al. (2009) reported on 24-month outcome for BRYAN cervical disc (Medtronic Sofamor Danek, Memphis, TN). 242 patients were randomized to the BRYAN cervical disc and 221 were in the control ACDF group. The rate of secondary surgical procedures at the treated level was 2.5% in the total disc replacement (TDR) patients and 3.6% in the fusion group though this was not statistically significant. Interestingly, composite overall success was achieved in 82.6% artificial disc patients and only 72.7% of fusion patients ($p = 0.010$). Another randomized, controlled IDE study by Mummaneni et al. (2007) enrolled 276 patients to arthroplasty with PRESTIGE ST cervical Disc System (Medtronic Sofamor Danek, Memphis, TN) and 265 patients to ACDF with 24-month follow-up. The groups showed similar improvement in validated outcome measures (NDI and VAS arm/neck pain scores), but the composite overall success rate was significantly higher at 24 months in the arthroplasty group than ACDF control group (79.3% vs. 67.8%, $p = 0.0053$). The reoperation rate in the arthroplasty group was lower (1.1% vs. 3.4%, respectively, $p = 0.0492$, log-rank test) for AS disease than the control group. Though these 2-year outcomes showed equivalence in this noninferiority statistical design and the effect on AS degeneration was promising, long-term studies of the effect on AS disease with motion preservation were still needed.

One of the earliest attempts to analyze AS disease following cervical artificial disc replacement was performed by Jawahar et al. (2010). In this study, a total of 93 patients were enrolled in 3 prospective randomized trials of artificial cervical discs. Patients showed equivalence in symptomatic relief (71% in TDA vs. 73.5% in ACDF). At last follow-up (median 36.4 months), 15% of patients with ACDF and 18% of TDA had clinical and radiographic AS disease which was not statistically different. A follow-up study by Nunley et al. (2012) included 170 patients with 3- and 4-year follow-up after treatment for 1 and 2-level cervical disc degeneration with cervical artificial disc or ACDF. AS degeneration and disease was reported in 16.5% of patients during follow-up ranging from 32 to 54 months (median 38 months)

though only 4.1% of patients required a second surgery at adjacent level. At 4 years, adjacent level degeneration-free rate was 76.7% in artificial disc group and 78.3% in the ACDF group, suggesting no difference in development of AS disease after arthroplasty.

Another study by Maldonado et al. (2011) prospectively studied 190 patients with a minimum of 3-year follow-up after ACDF or artificial disc to evaluate the incidence of AS degeneration. Radiographic evidence of AS degeneration was defined as new or enlarging anterior osteophytes or new or increased calcification of the anterior longitudinal ligament. AS degeneration was found in 10.5% of patients in the ACDF group and in 8.8% of patients in the arthroplasty group though this did not reach clinical significance ($p = 0.69$). This study did not address AS disease requiring operative intervention.

Another prospective, randomized IDE trial by Davis et al. (2015) followed 291 patients for 48 months after arthroplasty with MOBI-C cervical artificial disc (LDR Medical; Troyes, France) and ACDF. At 4-year follow-up, TDR group had significantly less AS degeneration than the ACDF group (41.5% vs. 89.5%, respectively, $p < 0.0001$). Re-operation at the index level was significantly lower for TDR group (4.0%) versus ACDF group (15.2%, $p < 0.0001$). Indication for TDR group re-operation was stenosis, device migration, poor endplate fixation, and persist neck and/or shoulder pain. The most common indication for re-operation in ACDF group was symptomatic pseudarthrosis. This study also did not address AS disease.

Studies addressing AS re-operation rate provide a more objective assessment of the effect of motion preservation on adjacent levels. In a single institution study by Coric et al. (2010) with 3 separate prospective randomized trials for artificial cervical discs, lower re-operation rates were observed for arthroplasty than fusion. 90 patients were randomized to ACDF (37 patients) or cervical disc arthroplasty (53 patients) with 2-year minimum follow-up (mean 38 months). Clinical success, defined as a composite measure of five separate components, was significantly higher in the arthroplasty group (85%) compared to the ACDF group (70%, $p = 0.035$). Adjacent level disease requiring re-operation occurred at a rate of 1.7% (0.5%/year) in the arthroplasty group which was lower (but not statistically significant) than the rate of 8.1% (2.6%/year) in the ACDF group. A multicenter randomized US FDA IDE trial also by Coric et al. (2011) addressed radiographic adjacent-level changes and re-operation rate. A total of 269 patients were enrolled with 135 patients randomized to TDR with the Kineflex-C disc and 133 to ACDF. There were no preoperative differences in the radiographic changes at adjacent levels. Radiographic deterioration was graded as none, mild, moderate, or severe. At 2-year follow-up, severe adjacent-level deterioration was evident in 24.8% of ACDF patients and only 9% in TDR group ($p < 0.0001$). Index-level re-operation rate was similar (5.0% TDR vs. 6.1% ACDF) and there was no significant difference in AS re-operation rate (7.6% for TDR and 6.1% for ACDF).

Given the low incidence of AS disease requiring re-operation, long term studies and large number of subjects are required to adequately assess the potential positive effect of motion preservation. A single institution study by Coric et al. included two devices (Bryan Disc or Kineflex/C) and enrolled 41 patients in CDR and 33 patients in ACDF control. A total of 63 patients had a minimum of 4-year follow-up. Both arthroplasty and ACDF patients showed a low rate of index level re-operation rate (2.4% vs. 0%, respectively) and adjacent level re-operation (4.9% vs. 3.0%, respectively) without statistically significant differences. Two studies have presented 7-year follow-up on arthroplasty outcomes. Vaccaro et al. (2013) reported a US FDA IDE trial of the SECURE-C device. At 24 months, patients in the arthroplasty group had statistically lower index level re-operations than ACDF (2.5% vs. 9.7%, respectively) and similar AS re-operation rate at 2-years (1.7% vs. 1.4% respectively). Recently, follow-up 7-year data was released that showed very significant differences in index and adjacent level re-operation rates. Index level re-operation rate was significantly lower in TDR group (4.2% vs. 15.3%). For AS re-operation rates, the incidence for cervical TDR was 4.2% compared to 16.0% in the ACDF group. Another long-term

7-year study by Burkus et al. (2014) reported on the efficacy of cervical disc replacement with Prestige Disc (Medtronic, Memphis, TN). 541 patients were randomized at 31 investigational sites to TDR or ACDF. At 84 months, surgery at the index level were lower for TDR than ACDF (4.8% vs. 13.7%, $p < 0.001$) as well as at adjacent levels (4.6% vs. 11.9%, $p = 0.008$).

Long term results have also been observed to be significant for 2 level cervical disc arthroplasty compared to ACDF. Radcliff et al. (2015) reported on 5-year results of TDR and ACDF for 2-level degenerative cervical disease. A total of 225 patients underwent 2-level TDR and 105 patients underwent 2 level ACDF. At 60-month follow-up, there were significantly fewer second surgeries in TDR group than in the ACDF group (71% vs. 21.0%, $p = 0.0006$). In regard to AS degeneration, there also were significantly less AS degeneration in TDR group than in the ACDF group (50.7% vs. 90.5%, $p < 0.0001$). Furthermore, there were significantly fewer AS reoperations in TDR group than in the ACDF group (3.1% vs. 11.4%, $p = 0.0004$). For TDR, the annual rate of AS re-operation was 0.6%/year which is similar to the actual re-operation rate (0.66%/year) reported by Hillebrand.

Radcliff et al. (2015) also reported on a "real-world" application of arthroplasty versus ACDF. A retrospective, matched cohort analysis of patients enrolled in a Blue Cross Plan assessed a "real-world" population with symptomatic cervical disease treated with TDR or ACDF. A total of 6635 patients in the ACDF group and 327 patients in the cervical TDR group. At 36 months, the incidence of reoperation at index level in TDR group was 5.7% compared to 10.5% in ACDF group ($p = 0.0214$). Further, AS re-operation rate was significantly lower for cervical TDR group compared to ACDF (3.1% vs. 11.4%, respectively). This study was performed outside of randomized trials and therefore represents "real world" outcomes supporting a lower incidence of index and adjacent level re-operation after cervical TDR than ACDF. Interestingly, this study also showed a significant reduction in all costs at 2 years of 12% in the TDR group ($34, 979 vs. ACDF $39,820).

Two meta-analysis have also addressed AS disease after cervical arthroplasty and ACDF. Upadhyaya et al. (2012) included 3 randomized, multicenter, US FDA IDE studies. A total of 621 patients received an artificial disc and 592 patients were treated with ACDF. At 24 months, 1098 patients were available for follow up. The rate of secondary surgery at the index level was significantly lower for arthroplasty with an RR of 0.44 (95% CI 0.26–0.77, $p = 0.004$, $I^2 = 0\%$). There was also a significant reduction in the adjacent-level reoperation risk favoring arthroplasty with an RR of 0.460 (95% CI 0.229–0.926, $p = 0.030$, $I^2 = 2.9\%$). McAfee et al. (2012) meta-analysis of the 3 FDA-approved TDR IDE studies above and PCM cervical disc (NuVasive Inc., San Diego, CA). A total of 1226 patients had a with minimum 2-year follow-up. Overall survivorship was defined as the absence of revision, reoperation, supplemental fixation, or device removal within 24-month follow-up period. Survivorship was achieved in 96.6% of arthroplasty patients (804 of 832) and 93.4% of ACDF patients (725 of 776). The difference in proportions was 3.2% (95% CI:1.1–5.3%, $P = 0.004$), suggesting that arthroplasty is superior to ACDF in regard to secondary surgical procedure. Unfortunately, this meta-analysis did not specifically address AS re-operation rate.

Conclusions

AS degeneration leading to re-operation is a multifactorial process. Factors contributing to the etiology of this process include: (a) the natural history of the underlying degenerative disease, (b) surgical technique, e.g., minimally invasive, muscle, and ligament sparing versus open procedures, (c) surgical decision-making, e.g., single versus multilevel surgery, (d) surgical procedure, i.e., fusion versus decompression alone versus arthroplasty, (e) patient specific factors such as overall sagittal balance. Due to inherently low incidence of AS re-operation following cervical spine surgery (<1%), long-term follow-up and/or large patient numbers are needed to demonstrate

statistically significant differences between procedures such as arthroplasty and fusion. Studies aim at detecting differences with only 2-year follow-up with less than several thousand patients are simply not powered to show statistically significant differences. Biomechanical studies have indicated cervical arthroplasty puts less stress on adjacent segments compared to fusion. Some prospective, randomized clinical studies indicate that arthroplasty decreases the rate of AS degeneration. Limited studies with long-term follow-up also support that arthroplasty may lead to less subsequent surgical intervention at index and adjacent segments. But continued long term data is required to confirm that this trend remains significant.

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