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A Prospective Randomized Controlled Trial Comparing Nano-Bioactive Glass plus Demineralized Bone Matrix (DBM) vs. DBM Alone in Single-Level ACDF with Standalone PEEK Cages

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Abstract:	Background Demineralized Bone Matrix (DBM) is commonly used in spinal fusion but is limited by donor variability and availability. Synthetic biologics such as bioactive glass (BAG) enhance graft containment and osteogenesis, potentially addressing these limitations. NanoFuse™ DBM, an FDA-approved combination of 45S5 BAG and DBM, offers a promising alternative to autograft. Preclinical studies suggest BAG accelerates DBM-induced bone formation. This is the first prospective randomized controlled trial (RCT) to compare DBM alone versus BAG+DBM in single-level anterior cervical discectomy and fusion (ACDF) using standalone PEEK cages. Methods Eighty-one patients undergoing single-level ACDF were randomized: Group 1 (n=44) received BAG+DBM; Group 2 (n=37) received DBM alone. Patients were followed for at least two years. Outcomes included radiographic fusion, Visual Analog Scale (VAS) for pain, and Neck Disability Index (NDI) for function.

	Results At six months, Group 1 achieved earlier fusion, while no fusion was observed in Group 2. By one year, both groups reached 100% fusion. Group 1 demonstrated significantly faster pain reduction (VAS 3.86 ± 2.43 at 6 months, P<0.001) compared to Group 2 (VAS 4.46 ± 2.53, P<0.001), with greater improvement at 12 months (P=0.043). NDI scores improved significantly in both groups. No non-unions, surgical complications, or revisions were reported; one patient in Group 1 required adjacent-level surgery. Conclusion BAG+DBM achieved earlier fusion and pain relief compared to DBM alone, supporting its use as a safe and effective alternative in ACDF. Clinical Relevance In ACDF, faster fusion and early pain relief are important for patient recovery and return to function. This study suggests that combining BAG with DBM may offer a clinically meaningful advantage without increasing surgical risk.
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Institutional Review Board (IRB) approval was granted for this study through Western Institutional Review Board (WIRB®) now known as WIRB-Copernicus Group (WCG® IRB) (WIRB#20181251).

Structured Abstract

Background: Demineralized Bone Matrix (DBM) is commonly used in spinal fusion but is limited by donor variability and availability. Synthetic biologics such as bioactive glass (BAG) enhance graft containment and osteogenesis, potentially addressing these limitations. NanoFuse™ DBM, an FDA-approved combination of 45S5 BAG and DBM, offers a promising alternative to autograft. Preclinical studies suggest BAG accelerates DBM-induced bone formation. This is the first prospective randomized controlled trial (RCT) to compare DBM alone versus BAG+DBM in single-level anterior cervical discectomy and fusion (ACDF) using standalone polyetheretherketone (PEEK) cages.

Methods: Eighty-one patients undergoing single-level ACDF were randomized: Group 1 (n=44) received BAG+DBM; Group 2 (n=37) received DBM alone. Patients were followed for at least two years. Outcomes included radiographic fusion, Visual Analog Scale (VAS) for pain, and Neck Disability Index (NDI) for function.

Results: At six months, Group 1 achieved earlier fusion, while no fusion was observed in Group 2. By one year, both groups reached 100% fusion. Group 1 demonstrated significantly faster pain reduction (VAS 3.86 ± 2.43, $P<0.001$) compared to Group 2 (VAS 4.46 ± 2.53, $P<0.001$) at 6 months, with greater improvement at 12 months ($P=0.043$). NDI scores improved significantly in both groups. No non-unions, surgical complications, or revisions were reported; one patient in Group 1 required adjacent-level surgery.

Clinical Relevance: In ACDF, faster fusion and early pain relief are important for patient recovery and return to function. This study suggests that combining BAG with DBM may offer a clinically meaningful advantage without increasing surgical risk.

Conclusion: BAG+DBM achieved earlier fusion and pain relief compared to DBM alone, supporting its use as a safe and effective alternative in ACDF.

Keywords: Cervical; NanoFuse™; Bioactive Glass; BAG; Demineralized Bone Matrix; DBM; Fusion; Anterior Cervical Discectomy and Fusion; ACDF; Synthetic Biologics; Donor.

Level of Evidence: 1

Introduction

Interbody fusion provides anterior column spinal stabilization for treating various spinal pathologies, including degenerative disc disease (DDD), herniated disc, spondylolisthesis, and deformity[1]. In the United States, interbody fusion is the most commonly performed spinal procedure, with over 400,000 cases annually[2]. Anterior cervical discectomy and fusion (ACDF) is a well-established and effective treatment for cervical DDD[3-12] , and demineralized bone matrix (DBM) has been shown to be both safe and effective for ACDF[13,14]. Propensity score-matched case-control studies have reported comparable outcomes in one- to two-level ACDF with and without cervical plating[15].

Autologous iliac crest bone graft remains the gold standard for spinal fusion due to its osteogenic, osteoconductive, and osteoinductive properties. However, harvesting morbidity and associated complications make it a less desirable option[16]. Synthetic biologics provide an alternative that can mimic the biological function of human tissue while minimizing immunogenicity and eliminating the risk of disease transmission. The rapid advancement of orthobiologics has led to the development of various allografts and synthetic grafts, including DBM, collagen, calcium phosphate (hydroxyapatite [HA] and β-tricalcium phosphate [β-TCP]), ceramics, calcium sulfates, biodegradable polymers, and bioactive glass[17-19]. DBM combined with local bone has been demonstrated to be an effective substitute for autograft, eliminating the need for iliac crest bone harvesting[20].

45S5 bioactive glass (BAG), developed by Professor Larry Hench at the University of Florida in 1969, promotes osteogenesis through the release of biologically active ions, facilitating bone formation and bonding to existing bone[21]. NanoFuse™ Biologics (NanoFuse Biologics LLC, Burlington, MA, USA) is the only U.S. Food and Drug Administration (FDA)-approved

osteobiologic that combines DBM with synthetic 45S5 BAG in a ceramic-based calcium phosphor-silicate particulate formulation coated with gelatin. Upon exposure to aqueous body fluids, this formulation forms a three-dimensional ultra-porous calcium hydroxyapatite matrix scaffold, releasing ions that promote angiogenesis, osteogenesis, and antimicrobial activity[18,19,22,23].

While extensive literature supports DBM use in standalone ACDF, clinical research on BAG+DBM remains limited, with no published clinical trials and only a few basic science studies evaluating its potential[18,24-26]. The objective of this study is to be the first to compare the safety, efficacy, and clinical and radiographic outcomes of DBM alone versus BAG+DBM in single-level ACDF using standalone polyetheretherketone (PEEK) cages. We hypothesize that BAG+DBM will achieve faster radiographic fusion than DBM alone at six months.

Methods

Data was prospectively collected from 81 patients who underwent single-level standalone anterior cervical discectomy and fusion (ACDF) by a single surgeon using the A-CIFT Solofuse® PEEK interbody cage device (LESSpine, Burlington, MA, USA) in an outpatient setting. Patient enrollment spanned from January 2018 to 2022, with all participants followed up for a minimum of two years.

Patients were randomized into two groups using block randomization. Group 1 consisted of 44 consecutive patients who underwent ACDF using NanoFuse™ DBM (nano-BAG+DBM), while the control Group 2 included 37 patients who underwent ACDF using DBM alone (DBM Pure, LESSpine Inc., Burlington, MA, USA). Scheduled follow-up visits were conducted within the first 2 weeks and at 3, 6, 12, and 24 months postoperatively.

Patients were considered for surgery after six months of persistent cervical radiculopathy and failure of conservative management, including physical therapy and pain management. Indications for ACDF surgery included symptomatic cervical spondylosis, herniated discs causing stenosis (Figure 1), degenerative disc disease with instability, myelopathy, radiculopathy, and facet arthritis. Exclusion criteria included acute severe trauma, fractures, malignancy, infection, unstable chronic medical conditions, a body mass index (BMI) >42[10,27], and prior anterior cervical fusions, anterior corpectomy, or total disc replacement. Preoperative assessment included the recommendation to discontinue narcotics at least two weeks prior to surgery for patients who had been on narcotics for more than six months[28]. Institutional Review Board (IRB) approval was granted for this study through the Western Institutional Review Board (WIRB®), now known as the WIRB-Copernicus Group (WCG® IRB) (WIRB#20181251). Informed consent was obtained from all individual participants.

ACDF Surgical Technique

Anterior cervical fusion was performed by modified approach to the standard Smith-Robinson operative technique[9,29]. A midline anterior cervical incision was made to achieve the surgical exposure of the desired vertebral level. Subcutaneous dissection was performed to allow adequate tissue mobilization. The posterior longitudinal ligament was retained *in situ* after total discectomy of the affected disc with pituitary ronguers, curette, and burr drills[30,31]. An appropriately sized standalone PEEK cage was measured, packed with bone graft, inserted, and fixated to the vertebrae by two screws, one cephalad and one caudal (Figure 2). In Group 1 patients, NanoFuse™ DBM was reconstituted into an injectable putty form by adding sterile normal saline to the granules. We used 2.5 cc of putty per level, which was placed within and anterior to the PEEK cage to aid with fusion (Figure 3A). For Group 2 patients, 2.5 cc of DBM

was placed within and anterior to the PEEK cage using a similar approach (Figure 3B). Once hemostasis was achieved, a Penrose drain was placed anterior to the spine for wound drainage for at least twenty- four hours.

Discharge and Outcomes

All patients were discharged within 2-4 hours of completing surgery after being deemed oriented and neurologically intact by the post-anesthesia care unit team, anesthesiologist, and operating surgeon. A protocol developed by the outpatient center, based on published literature, was used as the discharge criteria[32,33]. Patients were educated on potential complications, including dysphagia, transient-to-persistent soft tissue edema with possible airway compromise, postoperative hematoma, and infection[10].

Outcome measures for this study included both clinical and radiographic assessments. Clinical outcomes were assessed using the Visual Analog Scale (VAS) for neck pain and the Neck Disability Index (NDI) for functional disability. Plain radiographs (Figure 4) and computed tomography (CT) scans (Figure 5) were evaluated focused on bone fusion. Radiographic fusion was determined using the criteria outlined by Lebwohl et al., who identified bone bridging the interspace anterior to the cage on a lateral view as a clear indicator of fusion, termed the sentinel sign[34] . Fusion was defined as <1 mm of motion on plain radiographs, including flexion and extension views[35]. At least one of the locations (anterior, within, or posterior to the cage) confirmed the presence of continuous trabecular bone bridges on the plain lateral radiographs. Additional postoperative complications, revisions, and operative factors such as length of surgery (LOS) and estimated blood loss (EBL) were also recorded.

Statistical Analysis

Statistical analyses were conducted using Visual Studio (VS) Code (Version 1.87.1) and the anaconda3 (Python 3.12.0) kernel within VS Code, employing a comprehensive suite of Python coding and statistical packages including 'pandas', 'scipy.stats', 'matplotlib', and 'seaborn'. The Shapiro-Wilk Test confirmed that the data were normally distributed, which supported the use of parametric tests. Consequently, paired and independent samples t-tests were applied to identify statistically significant differences within groups and between groups.

Results

Demographics and Baseline Characteristics

Group 1 (nano-BAG+DBM) included 44 patients (59.1% female), with an average age of 44.9 ± 10.8 years and a mean Body Mass Index (BMI) of 32.3 ± 25.3 kg/m². Group 2 (DBM alone) comprised 37 patients (43.2% female), with an average age of 46.6 ± 9.7 years and a mean BMI of 30.8 ± 7.2 kg/m². Comparative analysis revealed no significant differences between the two groups in gender distribution (P = 0.348), age (P = 0.456), or BMI (P = 0.678). The total number of ACDF procedures performed at each spinal level is summarized in Table 1, with the illustrated in Figure 6.

Radiographic Fusion

At 6 months, Group 1 demonstrated earlier fusion within the interbody cage, whereas no fusion was observed in Group 2. By one year, both groups had achieved definitive fusion. At 12 months postoperatively, both groups demonstrated 100% fusion rates (Figures 4 and 5).

Pain and Functional Outcomes

Group 1 exhibited faster and greater pain reduction than Group 2. VAS scores in Group 1 improved from 7.77 ± 1.8 to 3.86 ± 2.43 at six months (P<0.001) and further decreased to 3.05 ±

2.35 at 12 months (P=0.031), followed by a reduction to 2.2 ± 2.37 at 24 months. In Group 2, VAS scores improved from 7.54 ± 1.98 to 4.46 ± 2.53 at six months (P<0.001) and to 4.08 ± 2.14 at 12 months (P=0.417). At 12 months postoperatively, Group 1 exhibited significantly greater pain improvement compared to Group 2 (P=0.043). No significant difference was observed in VAS scores between Group 1 and Group 2 preoperatively (P=0.583), at six months (P=0.284), or at 12 months (P=0.147).

NDI scores significantly improved in both groups. Group 1 showed a decrease from 49.7% (95% CI: 46.2%–53.2%) to 16.5% (95% CI: 14.7%–18.3%) (P<0.001), while Group 2 improved from 52.7% (95% CI: 49.2%–56.2%) to 15.2% (95% CI: 13.6%–16.8%) (P<0.001).

Surgical and Postoperative Outcomes

The length of surgery (LOS) and estimated blood loss (EBL) were comparable between groups. The mean LOS was 74.7 ± 33.6 minutes in Group 1 and 81.6 ± 32.3 minutes in Group 2, with no significant difference (P = 0.833). EBL was also similar, averaging 50.0 ± 0.0 cc in Group 1 and 48.8 ± 6.9 cc in Group 2 (P = 0.300). No non-unions, surgical complications, or revisions at the operated level were reported in either group. One patient in Group 1 required additional surgery for adjacent segment degeneration (ASD) at 14 months. There were no unplanned postoperative admissions due to pain or nausea, and no surgery-related complications were observed. However, one patient experienced an anesthesia-related incident (negative pressure pulmonary edema).

Discussion

Brief Summary and Purpose Of This Study

This study represents the first prospective randomized controlled trial (RCT) evaluating the combination of bioactive glass (BAG) and demineralized bone matrix (DBM) in standalone single-level ACDF procedures. While DBM alone has been widely used in spinal fusion due to its osteoinductive properties, synthetic biologics like BAG offer a novel approach to enhance fusion while reducing reliance on human donor tissue. This study fills an important gap by assessing whether BAG+DBM accelerates fusion, enhances pain relief, and improves functional recovery compared to DBM alone.

Summary of Key Findings

Our results demonstrated that Group 1 achieved earlier radiographic fusion within the interbody cage at 6 months, whereas no fusion was observed in Group 2 at that time point. By one year, both groups achieved definitive fusion with 100% fusion rates.

Clinically, nano-BAG+DBM resulted in faster and greater pain relief compared to DBM alone. Patients in the Group 1 showed significant improvement in pain scores as early as six months, while those in the Group 2 experienced a more gradual reduction. At 12 months, pain scores in the Group 1 were significantly lower, supporting the hypothesis that BAG accelerates bone healing and improves early patient-reported outcomes. However, by 24 months, pain levels in both groups were comparable, indicating that DBM alone still achieved effective long-term pain relief, albeit at a slower rate. Functional improvements followed a similar trend, with both groups showing significant reductions in disability scores, yet the BAG+DBM group demonstrated a more rapid return to function, particularly in the first 12 months. LOS and EBL were comparable between the two groups.

The safety profile of BAG+DBM was similar to DBM alone, with no reported non-unions, surgical complications, or revisions at the treated level. There were no unplanned postoperative

admissions due to pain or nausea, and complications were minimal, with only one patient in Group 1 requiring additional surgery for ASD and another experiencing an anesthesia-related incident.

Study Strengths and Comparison with Similar Research

Previous studies have supported the use of osteobiologics in promoting bone fusion, with autografts being the traditional gold standard[36,37]. However, autografts carry risks of morbidity, and DBM alone lacks the osteoconductive properties of autografts. Research on bioactive glass, particularly the 45S5 formulation, shows its ability to release ions that stimulate bone growth and integration, offering a more consistent alternative to DBM alone[21]. Our findings support existing research on BAG's osteoconductive and osteopromotive capabilities, which facilitate bone healing and structural integrity. This is consistent with Kirk et al.[18,22] who showed the biocompatibility and efficacy of bioactive glass in preclinical models. Pajamaki et al.[24-26] demonstrated in rat studies that the presence of bioactive glass with DBM accelerates bone induction. Unlike DBM, which can exhibit variability due to processing differences, BAG can be tailored for consistency, leading to predictable osteoconductive and osteoinductive propreties effects. Cottrill et al.[38] conducted a meta-analysis confirming that BAG enhances spinal fusion rates via its osteostimulatory effects, while maintaining a low risk of deep wound infections, positioning it as a viable substitute for DBM and autografts. Long-term clinical studies further validate BAG's efficacy. A four-year randomized controlled trial found that BAG spacers achieved fusion rates and clinical outcomes comparable to autologous bone grafts and titanium cages in single-level PLIF Another randomized trial reported similar fusion success between BAG spacers (89.7%) and titanium cages (91.2%) at 12 months post-surgery[39].

Limitations

The primary limitation of this study is its sample size and single-center design, which may limit the generalizability of the results to other surgical centers or patient populations. All procedures were performed by a single surgeon, which reduces variability but may not reflect the outcomes across different surgeons or institutions. Another limitation is the exclusive use of PEEK cages, which may have influenced the results, as different cage materials could yield varied outcomes.

Clinical Implications and Future Research

This study suggests that the combination of synthetic BAG+DBM is a promising and safe alternative to DBM alone in single-level ACDF procedures. The superior pain reduction observed in the BAG+DBM group, along with comparable fusion rates, highlights its potential to improve clinical outcomes. Moreover, this combination reduces reliance on human donor-derived DBM, optimizing resource use and addressing ethical concerns related to the availability and use of donor tissue.

Future research should focus on multi-center studies to validate these findings in a broader clinical setting and with a larger sample size to ensure reproducibility. Additionally, studies comparing the combination of bioactive glass and DBM with other synthetic biologics or autografts would further clarify the relative benefits of this approach. Long-term follow-up beyond two years will be critical in assessing the durability of fusion and the clinical outcomes over time.

Conclusion

This first prospective RCT evaluating the combination of bioactive glass (BAG) with DBM in ACDF demonstrates that NanoFuse™ DBM achieved fusion at 6 months, earlier than DBM alone, and resulted in significantly faster pain reduction. The VAS score for Group 1 was

significantly lower than for Group 2 at 12 months, and both groups achieved 100% fusion at one year. NDI scores also showed significant functional improvement in both groups. The earlier fusion and superior pain reduction in Group 1 may be attributed to the presence of BAG, aligning with preclinical findings that suggest BAG accelerates DBM-induced bone formation. Additionally, no non-unions, surgical complications, or revisions were reported, supporting the safety and viability of BAG+DBM as a fusion substrate. Our results further reinforce that BAG+DBM serves as an effective alternative to DBM alone, reducing reliance on cadaveric bone grafts while optimizing biologic graft utilization. Given its consistent osteoconductive properties, potential to enhance patient-reported outcomes, and ability to promote earlier bone formation without increasing surgical risks, BAG+DBM may emerge as a preferred option for cervical spine fusion procedures.

Footnotes:

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Figure Legend

Figure 1: Preoperative MRI scan showing a herniated disc at C5-6 causing cord compression.

Figure 2: Intraoperative photographs showing a single-level ACIFT standalone anterior cervical discectomy and fusion (ACDF).

Figure 3: Intraoperative photographs showing (A) NanoFuse™ DBM and (B) Demineralized Bone Matrix placed anterior to a standalone anterior cervical discectomy and fusion.

Figure 4: Postoperative lateral radiograph at 12 months showing solid fusion with (A) NanoFuse™ DBM and (B) Demineralized Bone Matrix.

Figure 5: Postoperative Computed topography (CT) showing solid fusion.

Figure 6: Total Number of anterior cervical discectomy and fusion procedures by spinal level.

Figure 1

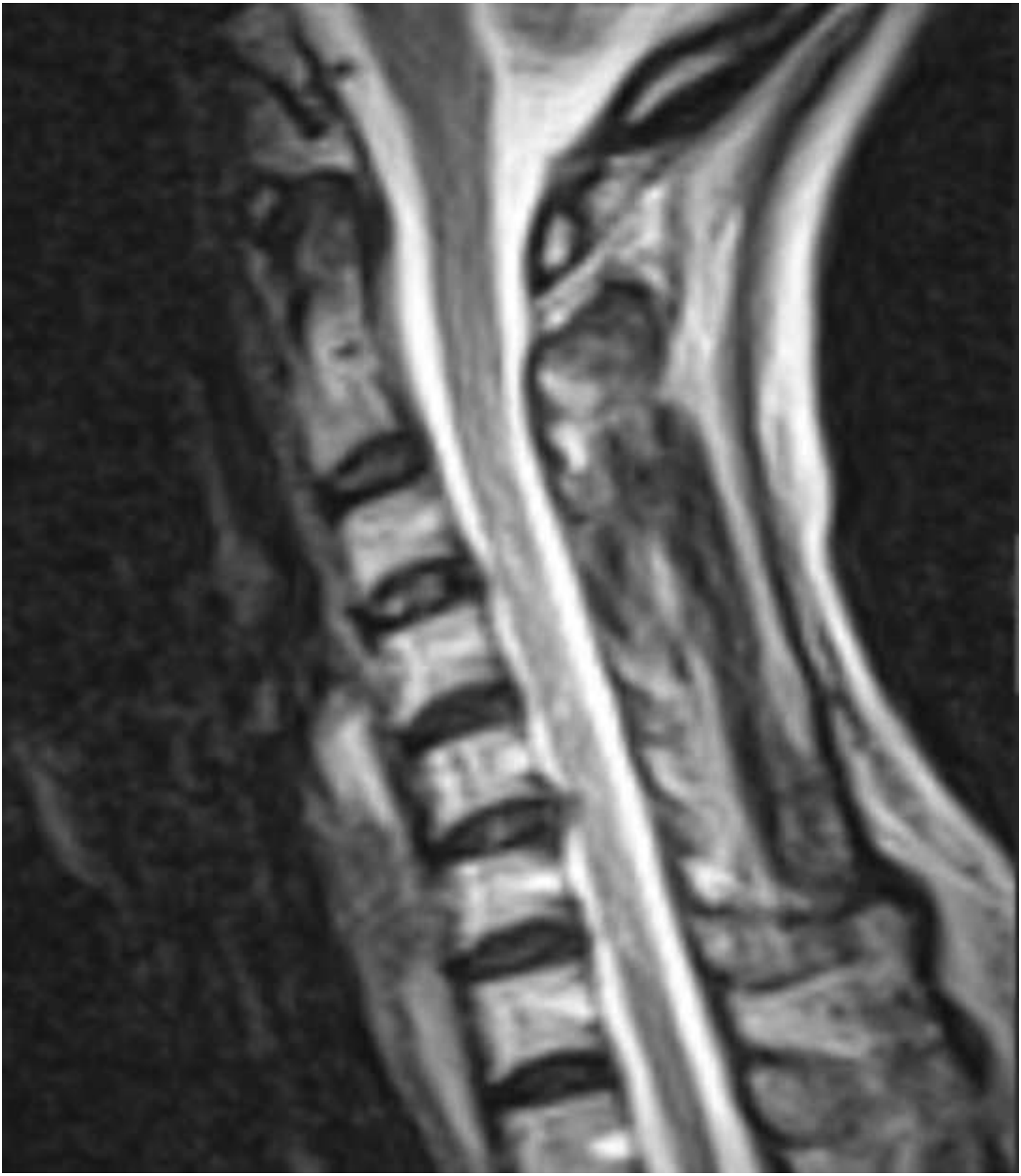

Figure 2

Figure 3

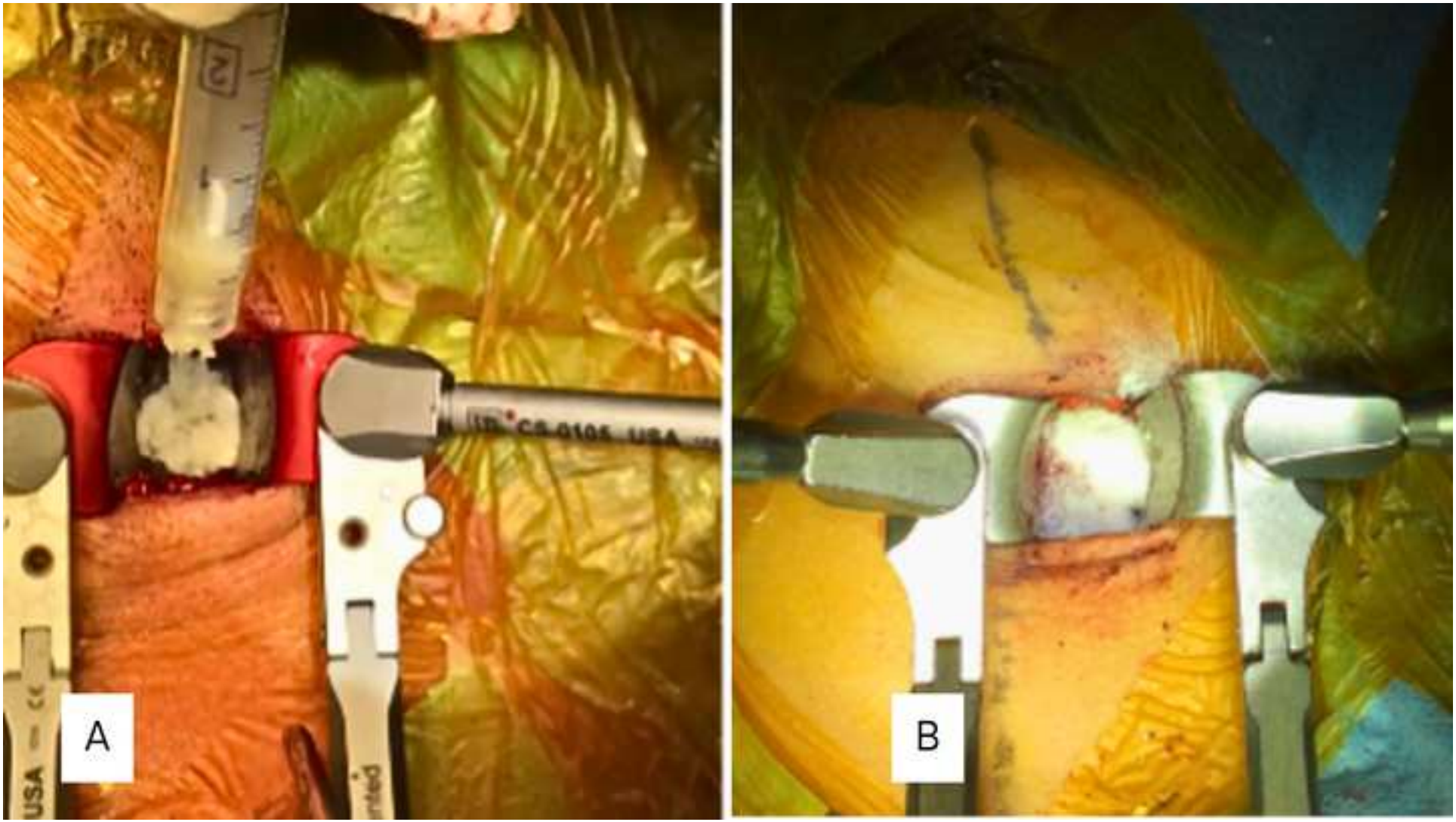

Figure 4

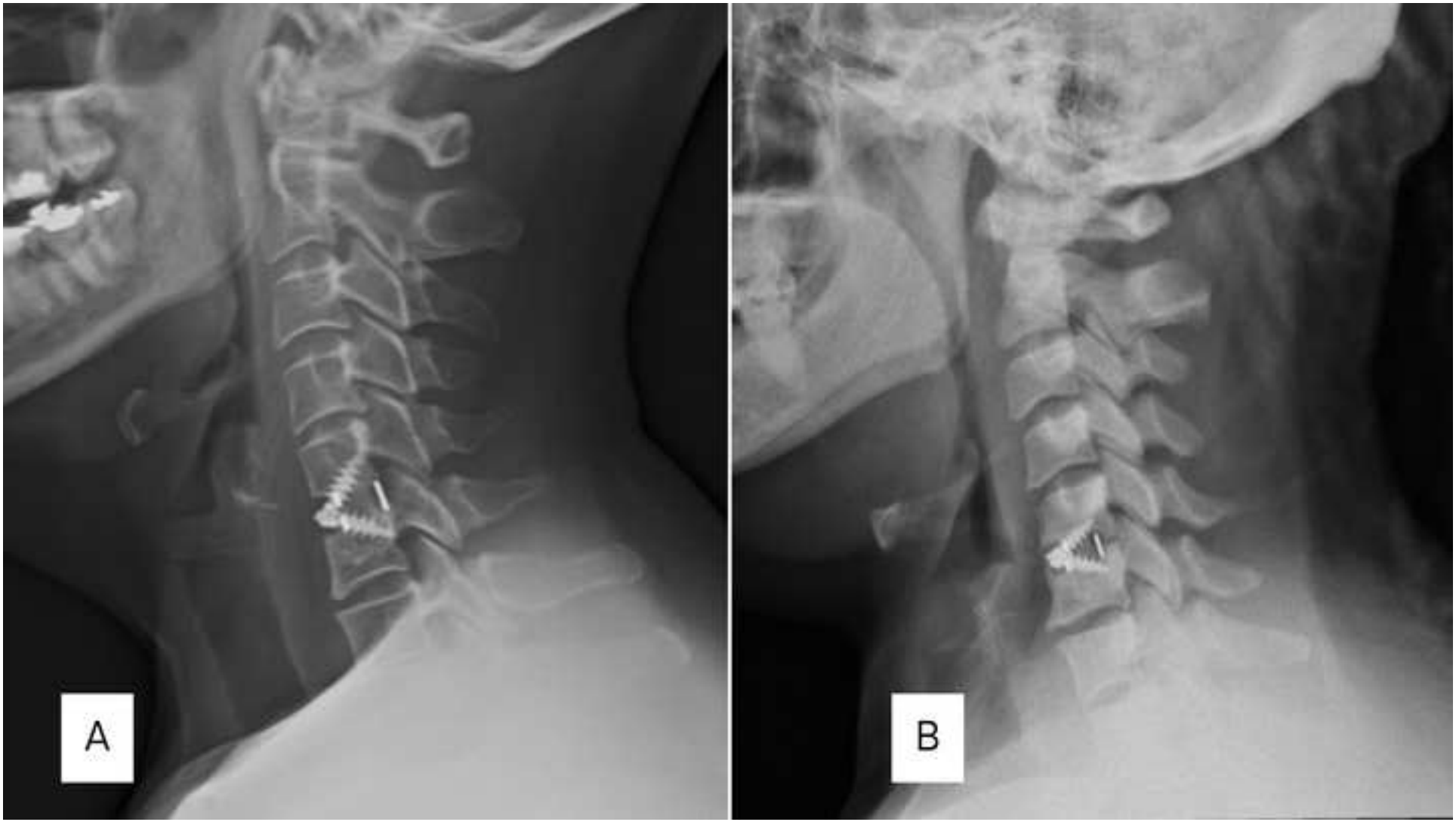

Figure 5

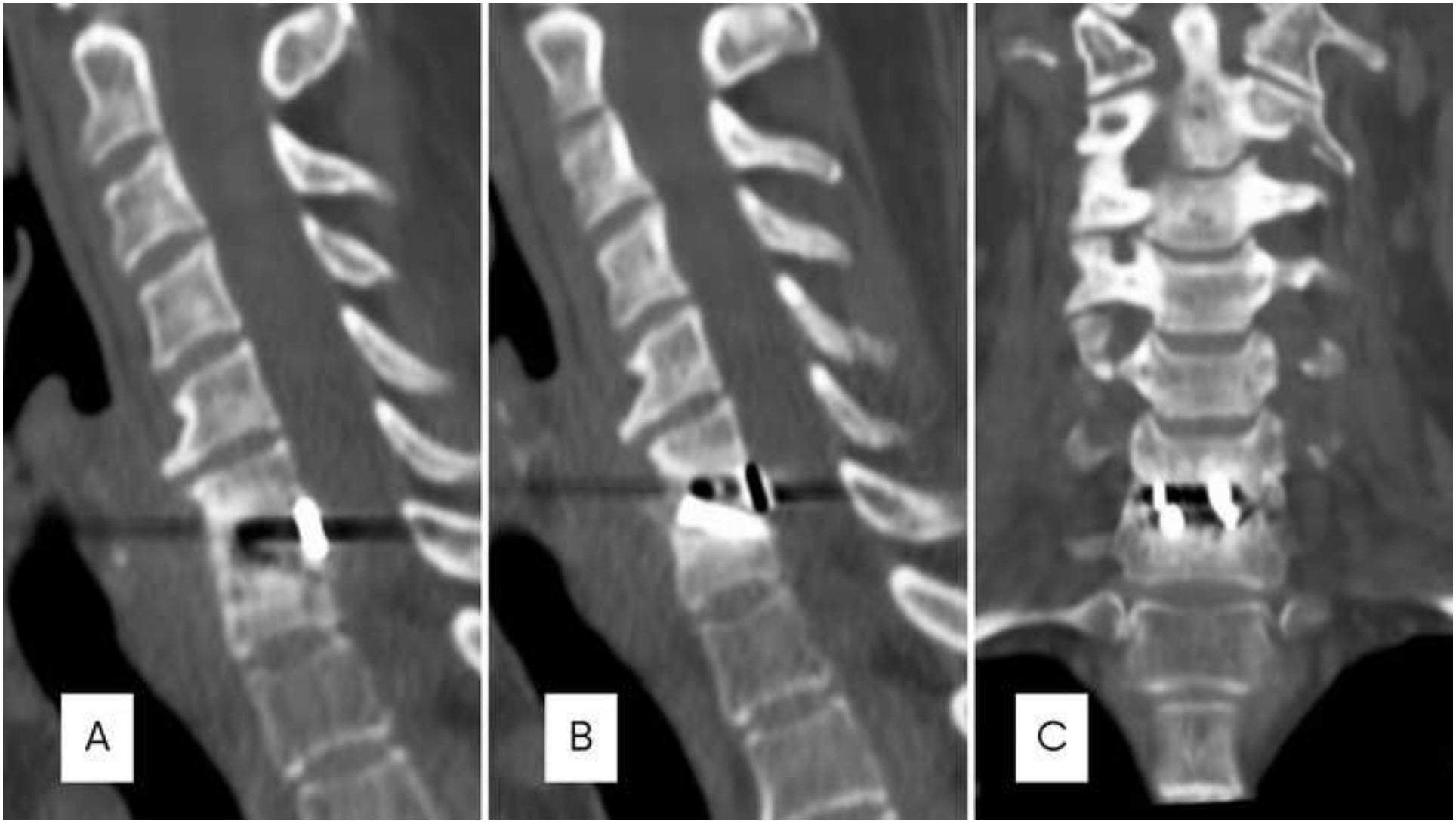

Figure 6

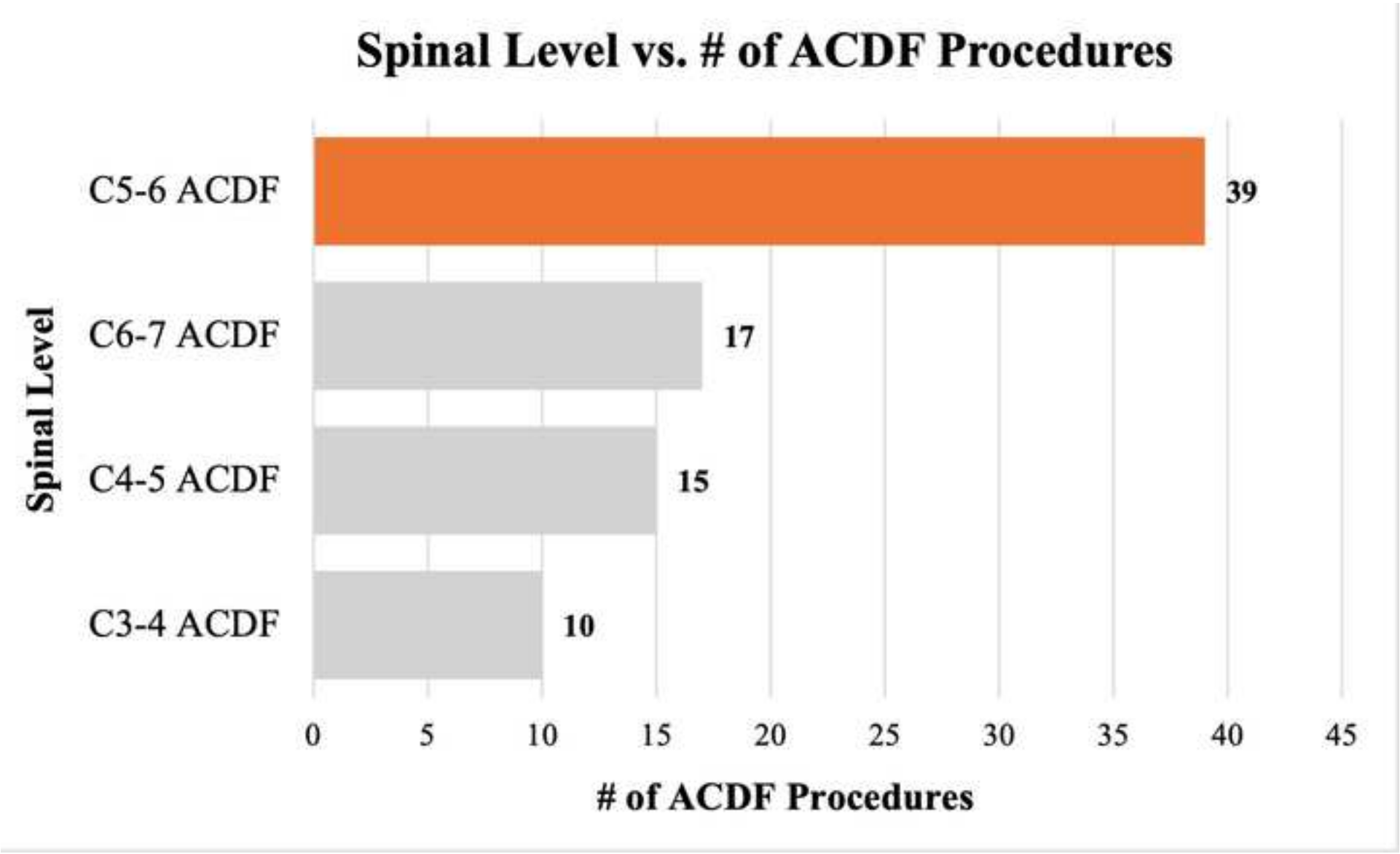
Spinal Level vs. # of ACDF Procedures
C5-6 ACDF
C6-7 ACDF
C4-5 ACDF
C3-4 ACDF
39
17
15
10
Spinal Level
0
5
10
15
20
25
30
35
40
45
# of ACDF Procedures

Table 1: Patient Demographics and Surgical outcomes

Variable	Group 1 (NF)	Group 2 (DBM)	P-Value
Patients (N)	44	37	0.437
Age (years)	44.9 ± 10.8	46.6 ± 9.7	0.326
BMI (kg/m^2)	32.3 ± 25.3	31.0 ± 7.2	0.345
Female	26 (59.1%)	16 (43.2%)	
Male	18 (40.9%)	21 (56.8%)	
LOS (minutes)	74.7 ± 33.6	78.5 ± 32.5	0.833
EBL (cc)	50.0 ± 0.0	48.8 ± 6.9	0.300
Mean ACDF Implant Size (mm)	6.6 ± 0.8	6.8 ± 0.8	0.266
Spinal Levels Treated			
C3-4	5	5	
C4-5	13	2	
C5-6	22	17	
C6-7	4	13	
Fusion Rate at 6 months	82%	0%	
Fusion Rate at 1 year	100%	100%	
Surgical Complications			
Non-Surgical complications	1 (Anesthesia related, negative pressure pulmonary edema)	0	
Revisions	0	0	

NF, NanoFuse™ Biologics; DBM, Demineralized Bone Matrix; BMI, Body Mass Index; ACDF; Anterior Cervical Discectomy and Fusion; LOS, Length of Surgery; EBL, Estimated Blood Loss