

AO Spine Guideline for the Use of Osteobiologics (AOGO) in Anterior Cervical Discectomy and Fusion for Spinal Degenerative Cases

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Abstract

Study design: Guideline

Objectives: To develop an international guideline (AOGO) about the use of osteobiologics in anterior cervical discectomy and fusion (ACDF) for treating degenerative spine conditions.

Methods: The guideline development process was guided by AO Spine Knowledge Forum Degenerative (KF Degen) and followed the Guideline International Network McMaster Guideline Development Checklist. The process involved 73 participants with expertise in degenerative spine diseases and surgery from 22 countries. Fifteen systematic reviews were conducted addressing respective key topics and evidence was collected. The methodologist compiled the evidence into GRADE Evidence-to-Decision frameworks. Guideline panel members judged the outcomes and other criteria and made the final recommendations through consensus.

Results: Five conditional recommendations were created. A conditional recommendation is about the use of allograft, autograft or a cage with an osteobiologic in primary ACDF surgery. Other conditional recommendations are about the use of osteobiologic for single- or multi-level ACDF, and for hybrid construct surgery. It is suggested that surgeons use other osteobiologics rather than human bone morphogenetic protein-2 (BMP-2) in common clinical situations. Surgeons are recommended to choose 1 graft over another or 1 osteobiologic over another primarily based on clinical situation, and the costs and availability of the materials.

Conclusion: This AOGO guideline is the first to provide recommendations for the use of osteobiologics in ACDF. Despite the comprehensive searches for evidence, there were few studies completed with small sample sizes and primarily as case series with inherent risks of bias. Therefore, high-quality clinical evidence is demanded to improve the guideline.

Keywords

osteobiologics, anterior cervical discectomy and fusion, AOGO, guideline, systematic review, autograft

Introduction

Osteobiologics are widely used in spinal surgeries, over a variety of indications including degenerative pathologies, deformities, trauma, and tumour.^{1,2} However, the clinical use of osteobiologics in spinal surgery is not very well defined and user guided. Several factors are responsible for the current

situation regarding osteobiologics. Firstly, there is a lack of high-quality clinical evidence for the use of biologics, which provides limited information to foster the knowledge and to guide the use of biologics. Secondly, regulations about the use of biologics vary highly across countries. The regulatory inconsistency further hinders the investigation of osteobiologics, especially their safety and efficacy. The fact is, in most

cases, the choice of a specific osteobiologic is dictated by surgeon's interest (familiarity, education and consulting) and/or hospital-approved inventory.

In the last couple of decades, there was an explosion of osteobiologics that aim to replace or enhance autograft use. A large number of studies focusing on lumbar and cervical degenerative cases have looked at the applicability of various graft materials. Demineralised bone matrix (DBM), synthetics and bone marrow aspirates (BMA) have been shown to have similar fusion rates to autograft or allograft; however, the level of evidence is low or limited depending on the indication.³⁻⁶ Human bone morphogenetic protein-2 (BMP-2) has been widely used for various approaches, while several complications have been associated with its use.

Among cervical spine degenerative disease surgical procedures, anterior cervical discectomy and fusion (ACDF) is commonly performed to alleviate symptoms and pain in patients which are unresponsive to conservative therapies.⁷ As fusion is considered one of the primary outcomes of ACDF, therefore, the graft choice is critical to achieve satisfactory fusion rate. In an international survey among spine surgeons on graft selection in ACDF, 74% voted for the use of non-structural graft material (allograft, autograft, BMA, DBM, platelet, ceramic and BMP2) for single-level and 72.8% use it for multi-level cases. Most used osteobiologics included local

graft (17%), autograft iliac crest (17%) followed by DBM (13%), allograft cancellous (8%) and ceramic (9%).⁸

Due to the paucity of the published clinical data, there is no consensus among spine surgeons regarding the osteobiologics to be used at single- or multi-level ACDF in a specific clinical scenario.

There is a need to develop an international guideline to provide spine community clarity on how and when to use osteobiologics in ACDF surgery.

Materials and Methods

The overall process of guideline development was guided by the AO policies and the Guideline International Network (GIN)-McMaster Guideline Development Checklist (<http://cebgrade.mcmaster.ca/guidecheck>). Detailed methods are published in a separate paper. The guideline group consisted of 73 people with expertise in degenerative spine diseases and surgery from 22 countries.

The guideline panel determined the topics for evidence review and outcomes to be assessed, including benefits (such as fusion and function) and harms (such as pain, medical and surgical complications), as well as resources, feasibility, acceptability and equity. There were 15 key topics (Table 1) covered in this guideline including the use of autograft,

Table 1. Systematic Review Topics of the AOGO Focus Issue.

Topic 1	Do osteobiologics augment fusion in ACDF surgery performed with mechanical interbody devices (PEEK, carbon fiber, metal cages) and is the fusion rate comparable to that with autograft? – A Systematic Review
Topic 2	Structural Allograft Versus Mechanical Interbody Devices Augmented with Osteobiologics in Anterior Cervical Discectomy and Fusion: A Systematic Review
Topic 3	The role of osteobiologics in augmenting spine fusion in unplated anterior cervical discectomy and fusion compared to plated constructs: A systematic review and meta-analysis
Topic 4a	Does the use of Autograft influence the Fusion and Complication Rates in patients undergoing 1 or 2-level Anterior Cervical Discectomy and Fusion Surgery? A PRISMA-compliant Network Meta-Analysis
Topic 4b	Complications of the use allograft in 1- or 2-level anterior cervical discectomy and fusion: A systematic review
Topic 4c	Complications with Demineralized Bone Matrix, Hydroxyapatite, and Beta-Tricalcium Phosphate in Single and Two-level Anterior Cervical Discectomy and Fusion Surgery
Topic 4d	Analysis of Complications in Multilevel Anterior Cervical Discectomy and Fusion using Osteobiologics other than Bone Morphogenetic Protein: A Systematic Review
Topic 5	Comparative Complications Associated with BMP Use in Patients Undergoing ACDF for Degenerative Spinal Conditions: Systematic Review and Meta-Analysis
Topic 6	The Use of Osteobiologics in Single Versus Multi-Level Anterior Cervical Discectomy and Fusion: A Systematic Review
Topic 7	The evidence for the use of osteobiologics in hybrid constructs (Anterior Cervical Discectomy and Fusion (ACDF) and total disc replacement (TDR)) in multilevel cervical degenerative disc disease: A systematic review
Topic 8	Dosing Strategy For Osteobiologics Used In ACDF Surgery, Influence On Fusion Rates And Associated Complications: An Up-to-date Systematic Literature Review and Meta-Analysis
Topic 9	Cervical Spine Fusion – Comparison of Different Osteobiologics and Different Imaging Modalities and Time Frames for Fusion Assessment
Topic 10	What is the evidence surrounding the cost-effectiveness of osteobiologic use in ACDF surgery? A systematic review of the literature
Topic 11	How Do Patient Comorbidities Affect the Choice of Osteobiologics for Anterior Cervical Discectomy and Fusion? – a Systematic Review
Topic 12	What is the Evidence Supporting Osteobiologic Use in Revision Anterior Cervical Discectomy and Fusion?

allograft or cage with osteobiologic in primary or revision ACDF surgery for degenerative conditions (single or multi-level) and in ACDF–TDR hybrid construct surgery. Applicable to all topics was whether graft choice would vary based on comorbidities. Systematic reviews of the evidence were conducted for each topic and are published separately. The methodologist compiled the evidence from the systematic reviews into GRADE Evidence-to-Decision (EtD) frameworks, using the GRADEpro Guideline Development Tool (www.gradeapro.org). The guideline panel provided feedback for each draft EtD framework via GRADEpro Panel Voice and comments were discussed during in-person and virtual meetings to make recommendations. Final recommendations were determined through consensus of the guideline panel members. The final guideline was reviewed by the guideline panel, the systematic review teams, and external reviewers. Final EtDs are available as a supplementary material (Supplementary material 1).

Each recommendation is defined as a strong or conditional recommendation according to the GRADE approach (<https://gdt.gradeapro.org/app/handbook/handbook.html>). Strong recommendations were made when desirable consequences clearly outweighed undesirable consequences and conditional recommendations when desirable consequences probably outweighed undesirable consequences. Strong recommendations are worded as ‘we recommend’ and most surgeons should follow the recommended action, and conditional recommendations are ‘we suggest’ and surgeons should likely follow the recommended action but recognise that different choices will be appropriate for each individual.

Recommendations

Autograft Versus Cage With Osteobiologic

Conditional recommendation based on low certainty evidence.

In primary ACDF surgery for degenerative conditions, we suggest that either structural iliac crest autograft or a cage with an osteobiologic (such as tricalcium phosphate, demineralised bone matrix, hydroxyapatite or allograft) can be used with similar outcomes.

Remarks. This recommendation applies to the use of different cages such as PEEK or titanium but does not address the use of morselised autograft (bone dust) in a cage. The choice of iliac crest autograft or cage plus osteobiologic may be dependent on availability, current costs and resources, which may vary with the institution and clinical situation (such as in patients with comorbidities). However, there is little to guide the use of autograft, cage or osteobiologic based on comorbidities. It is important to discuss donor site morbidity with patients when using autograft.

Summary of the Evidence. We conducted a systematic review of studies published up to October 2020 comparing the use of

autografts to the use of mechanical interbody devices augmented with osteobiologics (Table 1, Topic 1). There were 2 randomised controlled trials (both using a titanium device with either human cancellous allograft or hydroxyapatite coating) and 6 non-randomised studies (most using a PEEK device but also titanium with tricalcium phosphate).^{9–16} DBM was not assessed in the studies. Across all studies, there were little to no differences in fusion (from 12 to 0% in favour of autograft). The incidence of reoperations was also similar between autograft and osteobiologics across all studies (difference of 3–4%). Pain was measured in 3 studies^{10,13,14} and function in 4 studies,^{9,13–15} all showed little to no differences between autograft and osteobiologics. Neurological, soft tissue and surgical complications were reported together in most trials. From the RCTs (n = 375), there was no difference in complications.^{10,13} However the non-randomised studies (n = 392) found slightly more complications with autograft (8.9% vs 4.4%); these studies were at higher risk of bias.^{9,11,12,14–16} When using autograft, donor site morbidity may occur. In RCTs, the incidence was 8% (14/172), but it was 22% (24/107) in non-randomised studies.^{10–16} A systematic review was also conducted for cost-effectiveness (Table 1, Topic 10) and found that costs were variable across studies and appeared to be locally dependent. There was no data to inform the use of different osteobiologics in patients with different comorbidities. Overall, evidence suggests that the benefits and harms are similar when using autograft or a device plus osteobiologic, with the exception of donor site morbidity with autograft (low certainty evidence).

Allograft Versus Cage With Osteobiologic

Conditional recommendation based on very low certainty evidence.

In primary ACDF surgery for degenerative conditions, we suggest either allograft or a cage with an osteobiologic depending on factors such as availability, costs and resources.

Remarks. Because of the lack of evidence for differences in benefits, other factors will play a greater role in choice of allograft or cage. Factors may vary based on availability of allograft, with the institution and clinical situation (such as in patients with comorbidities). However, there is little to guide the use of allograft, cage or osteobiologic based on comorbidities.

Summary of Evidence. We conducted 3 systematic reviews of studies published up to October 2020: 1 included study comparing the use of allografts to the use of mechanical interbody devices augmented with osteobiologics (Table 1, Topic 2); the other review included studies assessing effects of allograft only (Table 1, Topic 4b); and, the other review included studies assessing complications of mechanical interbody devices augmented with osteobiologics only (Table 1, Topic 4c). Three studies compared allograft to ceramic glass or

DBM;^{17–19} 2 (n = 110) were at lower risk of bias and found trivial differences in fusion (0–14% at 1 year and 3% at 2 years).^{17,18} In these 2 comparative studies, fusion occurred in 73% and 100% with osteobiologics, which was similar to the range (68.5–100%) reported when using allograft in 14 non-comparative studies (n = 1455). One study (n = 71) measured pain (VAS, 0–10, worse), pain was reduced by 2 points with allograft and 1.2 points with osteobiologic.¹⁸ Complications were inconsistent across the comparative studies. However, across 18 non-comparative studies, complications occurred in similar numbers for dysphagia/dysphonia (.4–22%), wound-related complications (0–7%), new neurologic deficit (0–1.9%) and post-operative radiculopathy (0–2%) (Table 1, Topic 4b and Topic 4c). Overall, evidence suggests that the benefits (such as fusion) and harms (such as complications) are similar when using allograft or a cage with osteobiologic, but this evidence is of very low certainty. The costs were variable across studies and appear to be locally dependent, but costs for cell-based allografts may be relatively higher in most institutions (Table 1, Topic 10). There was no data to inform the use of different osteobiologics in patients with different comorbidities.

Use of BMP-2

Conditional recommendation based on very low certainty evidence.

When using a cage with osteobiologic in ACDF surgery, we suggest osteobiologics other than BMP in common clinical situations.

Remarks. There may be clinical situations where BMP-2 may be a reasonable choice. However, given the potential increase in harms, close monitoring for anterior soft tissue complications (such as dysphagia) is warranted when used.

Summary of Evidence. A systematic review was conducted and included 12 non-comparative studies assessing the use of BMP and 9 studies comparing BMP to autograft, allograft or other osteobiologics in ACDF surgery (Table 1, Topic 5). Studies of large retrospective databases where biases in the reporting of outcomes may occur were not included in the development of the recommendation. There may be no difference in fusion with BMP at doses > or <.75 mg/level or with autograft, allograft or other osteobiologics (~98% and ~87%, respectively). However, there may be slightly more complications with BMP-2, such as dysphagia/dysphonia and other soft tissue complications regardless of dose (26% vs 21% and 27% vs 20%, respectively). Other complications may be similar or slightly lower with BMP-2, including medical, neurological and failure-related complications. The effect of dosage of BMP-2 was inconsistent across complications. Overall, few studies exist that assess the effects of BMP-2 in ACDF surgery resulting in very low certainty evidence. Although the use of BMP-2 is feasible, BMP-2 is relatively more expensive than other osteobiologics, and these costs may not outweigh any perceived benefits in common clinical situations.

Single- or Multi-Level Surgery

Conditional recommendation based on low certainty evidence in effects

We suggest that an osteobiologic can be used in single- or multi-level primary ACDF surgery for degenerative conditions.

Remarks. Surgeons may decide to use osteobiologics in single- or multi-level fusion based on clinical situation. The choice of osteobiologic may be dependent on factors such as availability, institution and clinical situation.

Summary of Evidence. We conducted a systematic review and found 8 studies^{18,20–26} comparing the use of osteobiologics and autograft or allograft in single- vs multi-level ACDF, and there was however very limited data for ≥ 3 levels (Table 1, Topic 6). Studies reported no differences in fusion or in patient-reported outcomes, such as pain or function. Information about complications comes primarily from studies that are non-comparative. In a systematic review of studies assessing allograft and studies assessing osteobiologics, complications were similar: dysphagia/dysphonia occurred in ACDF with single- or two-levels in 0–14% with allograft vs 1–22% with osteobiologic; wound-related complications in 0–2% (5 studies, n = 696) with allograft and 23% (43/188) in another study vs 0–7% (8 studies, n = 647) (Table 1, Topic 4b and Topic 4c). Other complications were typically <3% with allograft or osteobiologic at single- or two-levels. There were also very few to no complications with osteobiologics in 3-level ADCF in 3 studies (n = 96).^{27–29} In other studies reporting the use of osteobiologics in multi-level surgery the graft material used was heterogeneous – a mix of autograft, allograft and/or osteobiologic and complications could not be synthesised.^{30–33} Overall, there is low certainty evidence that the benefits (such as fusion) and complications are similar in single- or multi-level ACDF surgery when using osteobiologics. The costs are variable across studies and appear to be locally dependent.

ACDF–TDR Hybrid Construct Surgery

Conditional recommendation based on very low certainty evidence.

In ACDF–TDR hybrid construct surgery for degenerative conditions, we suggest for the fusion level using either structural iliac crest autograft or allograft or a cage with osteobiologic (such as DBM, bovine bone or BMP-2) to achieve similar outcomes.

Remarks. The choice of iliac crest autograft or allograft or osteobiologics may be dependent on availability, current costs and resources which may vary with the institution and clinical situation (such as in patients with comorbidities). However, there is little to guide their use based on comorbidities.

Summary of Evidence. A systematic review was conducted by Hoelen et al to compare the effects of using an osteobiologic vs none (or autograft or allograft) in hybrid surgery (Table 1, Topic 7). They searched for studies published between 2000 and 2021 and found 7 studies.^{34–40} No study directly compared hybrid surgery using an osteobiologic compared to allograft or autograft but instead compared hybrid surgery to ACDF or TDR alone. Most of the studies (5/7) were conducted in Asia: 3 in China^{37,39,40} and 1 in South Korea reported in 2 publications.^{36,38} One study was conducted in Italy³⁴ and another in the USA.³⁵ Fusion (n = 99) was 88% (with BMP) and 100% (with bovine bone) vs 100% with allogenic bone. Range of motion (C2–C7) was reduced by 6.8° and 11.1° with osteobiologics vs reduced by 2.7° and increased by 1.28° with iliac and allogenic bone. There were similar reductions in neck and arm pain (range from 3.4 to 6.5) and in the Neck Disability Index (range 18% to 47%) with osteobiologic vs iliac or allogenic bone. Few studies reported complications, but when reported proportions were similar with the use of osteobiologics or not in hybrid construct surgery. Costs are variable across studies and appear to be locally dependent. Overall, benefits (such as fusion) may be similar when using an osteobiologic or autograft or allograft in hybrid construct surgery, and evidence does not suggest that there are greater complications when using osteobiologics. However, the evidence is very uncertain.

Revision Surgery

No recommendation was made for the use of osteobiologics in revision surgery because evidence was not identified.

Conclusions and Usage

Despite the comprehensive review of evidence, there were often few studies with small sample sizes and primarily non-randomised studies and case series with inherent risks of bias, and therefore, the certainty of the evidence for the benefits and harms, and the costs was low or very low. Additionally, no information on comorbidities or risk factors was available. Although our certainty in the evidence will likely increase over time with new studies, at present, we do have some evidence that harms are not increased with the use of osteobiologics in common clinical situations. For this reason, the guideline group suggested the use of autograft, allograft, or cage with an osteobiologic. This means that surgeons can choose to use 1 graft over another or 1 osteobiologic over another primarily based on clinical situation, and the costs and availability of the materials. In such cases, surgeons will need to be informed of their local situation when making decisions.

The development of this guideline also has implications for future research with well-controlled study groups and defined outcomes. As the evidence on osteobiologics grows, the AOGO will update this guideline to reflect new advancements and

evidence. KF Degenerative is leading a separate effort on a global prospective clinical study and collecting the evidence on the use and effects of osteobiologic in ACDF and other spine surgeries.

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Supplemental Material

Supplemental material for this article is available online.

References

1. Aghdasi B, Montgomery SR, Daubs MD, Wang JC. A review of demineralized bone matrices for spinal fusion: The evidence for efficacy. *Surgeon*. 2013;11(1):39–48.
2. Yoon ST, Boden SD. Spine fusion by gene therapy. *Gene Ther*. 2004;11(4):360–367.
3. Buser Z, Brodke DS, Youssef JA, et al. Synthetic bone graft versus autograft or allograft for spinal fusion: A systematic review. *J Neurosurg Spine*. 2016;25(4):509–516.
4. Buser Z, Hsieh P, Meisel HJ, et al. Use of autologous stem cells in lumbar spinal fusion: A systematic review of current clinical evidence. *Global Spine J*. 2021;11(8):1281–1298.
5. Hsieh PC, Buser Z, Skelly AC, et al. Allogenic stem cells in spinal fusion: A systematic review. *Global Spine J*. 2019;9(1 suppl 1):22S–38S.
6. Hsieh PC, Chung AS, Brodke D, et al. Autologous stem cells in cervical spine fusion. *Global Spine J*. 2021;11(6):950–965.

7. An HS, Simpson JM, Glover JM, Stephany J. Comparison between allograft plus demineralized bone matrix versus autograft in anterior cervical fusion. A prospective multicenter study. *Spine (Phila Pa 1976)*. 1995;20(20):2211-2216.
8. Yoon ST, Konopka JA, Wang JC, et al. ACDF graft selection by surgeons: Survey of AOSpine members. *Global Spine J*. 2017;7(5):410-416.
9. Ahn JS, Lee JK, Kim JH. Comparative study of clinical outcomes of anterior cervical discectomy and fusion using autograft or cage with bone substitute. *Asian Spine J*. 2011;5(3):169-175.
10. Bärlocher CB, Barth A, Krauss JK, Binggeli R, Seiler RW. Comparative evaluation of microdiscectomy only, autograft fusion, polymethylmethacrylate interposition, and threaded titanium cage fusion for treatment of single-level cervical disc disease: a prospective randomized study in 125 patients. *Neurosurg Focus*. 2002;12(1):E4.
11. Bhadra AK, Raman AS, Casey AT, Crawford RJ. Single-level cervical radiculopathy: Clinical outcome and cost-effectiveness of four techniques of anterior cervical discectomy and fusion and disc arthroplasty. *Eur Spine J*. 2009;18(2):232-237.
12. Chou YC, Chen DC, Hsieh WA, et al. Efficacy of anterior cervical fusion: Comparison of titanium cages, polyetheretherketone (PEEK) cages and autogenous bone grafts. *J Clin Neurosci*. 2008;15(11):1240-1245.
13. Hacker RJ, Cauthen JC, Gilbert TJ, Griffith SL. A prospective randomized multicenter clinical evaluation of an anterior cervical fusion cage. *Spine (Phila Pa 1976)*. 2000;25(20):2646-2654.
14. Huh J, Oh JY, Chough C, Cho C, Joo W, Park H. Polyetheretherketone cage filled with beta-tricalcium phosphate versus autogenous tricortical iliac bone graft in anterior cervical discectomy and fusion. *Korean J Spine*. 2011;8(3):165-171.
15. Sharma A, Kishore H, Singh V, et al. Comparative study of functional outcome of anterior cervical decompression and interbody fusion with tricortical stand-alone iliac crest autograft versus stand-alone polyetheretherketone cage in cervical spondylotic myelopathy. *Global Spine J*. 2018;8(8):860-865.
16. Vanek P, Bradac O, DeLacy P, Saur K, Belsan T, Benes V. Comparison of 3 fusion techniques in the treatment of the degenerative cervical spine disease. Is stand-alone autograft really the "gold standard"? Prospective study with 2-year follow-up. *Spine (Phila Pa 1976)*. 2012;37(19):1645-1651.
17. Chen F, He W, Mahaney K, et al. Alternative grafts in anterior cervical fusion. *Clin Neurol Neurosurg*. 2013;115(10):2049-2055.
18. Kim HC, Oh JK, Kim DS, et al. Comparison of the effectiveness and safety of bioactive glass ceramic to allograft bone for anterior cervical discectomy and fusion with anterior plate fixation. *Neurosurg Rev*. 2020;43(5):1423-1430.
19. Teton ZE, Cheaney B, Obayashi JT, Than KD. PEEK interbody devices for multilevel anterior cervical discectomy and fusion: Association with more than 6-fold higher rates of pseudarthrosis compared to structural allograft. *J Neurosurg Spine*. 2020;32:696-702.
20. Agrillo U, Mastronardi L, Puzzilli F. Anterior cervical fusion with carbon fiber cage containing coralline hydroxyapatite: Preliminary observations in 45 consecutive cases of soft-disc herniation. *J Neurosurg*. 2002;96(3 suppl 1):273-276.
21. Dai LY, Jiang LS. Anterior cervical fusion with interbody cage containing beta-tricalcium phosphate augmented with plate fixation: A prospective randomized study with 2-year follow-up. *Eur Spine J*. 2008;17(5):698-705.
22. Eastlack RK, Garfin SR, Brown CR, Meyer SC. Osteocel Plus cellular allograft in anterior cervical discectomy and fusion: evaluation of clinical and radiographic outcomes from a prospective multicenter study. *Spine (Phila Pa 1976)*. 2014;39(22):E1331-E1337.
23. McAnany SJ, Ahn J, Elboghdady IM, et al. Mesenchymal stem cell allograft as a fusion adjunct in one- and two-level anterior cervical discectomy and fusion: a matched cohort analysis. *Spine J*. 2016;16(2):163-167.
24. Peppers TA, Bullard DE, Vanichkachorn JS, et al. Prospective clinical and radiographic evaluation of an allogeneic bone matrix containing stem cells (Trinity evolution® viable cellular bone matrix) in patients undergoing two-level anterior cervical discectomy and fusion. *J Orthop Surg Res*. 2017;12(1):67.
25. Topuz K, Colak A, Kaya S, et al. Two-level contiguous cervical disc disease treated with peek cages packed with demineralized bone matrix: Results of 3-year follow-up. *Eur Spine J*. 2009;18(2):238-243.
26. Xie Y, Li H, Yuan J, Fu L, Yang J, Zhang P. A prospective randomized comparison of PEEK cage containing calcium sulphate or demineralized bone matrix with autograft in anterior cervical interbody fusion. *Int Orthop*. 2015;39(6):1129-1136.
27. Chang WC, Tsou HK, Chen WS, Chen CC, Shen CC. Preliminary comparison of radiolucent cages containing either autogenous cancellous bone or hydroxyapatite graft in multi-level cervical fusion. *J Clin Neurosci*. 2009;16(6):793-796.
28. Park HW, Lee JK, Moon SJ, Seo SK, Lee JH, Kim SH. The efficacy of the synthetic interbody cage and grafton for anterior cervical fusion. *Spine (Phila Pa 1976)*. 2009;34(17):E591-E595.
29. Wang MY, Liu CY. Resorbable polylactic acid interbody spacers with vertebral autograft for anterior cervical discectomy and fusion. *Neurosurgery*. 2005;57(1):135-140.
30. Kim S, Alan N, Sansosti A, Agarwal N, Wecht DA. Complications after 3- and 4-level anterior cervical discectomy and fusion. *World Neurosurg*. 2019;130:e1105-e1110.
31. Laratta JL, Reddy HP, Bratcher KR, McGraw KE, Carreon LY, Owens RK 2nd. Outcomes and revision rates following multilevel anterior cervical discectomy and fusion. *J Spine Surg*. 2018;4(3):496-500.
32. Papadopoulos EC, Huang RC, Girardi FP, Synnott K, Cammisa FP Jr. Three-level anterior cervical discectomy and fusion with plate fixation: radiographic and clinical results. *Spine (Phila Pa 1976)*. 2006;31(8):897-902.
33. Wewel JT, Kasliwal MK, Adogwa O, Deutsch H, O'Toole JE, Traynelis VC. Fusion rate following three- and four-level ACDF

- using allograft and segmental instrumentation: A radiographic study. *J Clin Neurosci*. 2019;62:142-146.
34. Barbagallo GM, Assietti R, Corbino L, et al. Early results and review of the literature of a novel hybrid surgical technique combining cervical arthrodesis and disc arthroplasty for treating multilevel degenerative disc disease: Opposite or complementary techniques? *Eur Spine J*. 2009;18 Suppl 1(suppl 1):29-39.
35. Cardoso MJ, Mendelsohn A, Rosner MK. Cervical hybrid arthroplasty with 2 unique fusion techniques. *J Neurosurg Spine*. 2011;15(1):48-54.
36. Ji GY, Oh CH, Shin DA, et al. Artificial disc replacement combined with fusion versus 2-level fusion in cervical 2-level disc disease with a 5-year follow-up. *Clin Spine Surg*. 2017;30(5):E620-E627.
37. Kang L, Lin D, Ding Z, Liang B, Lian K. Artificial disc replacement combined with midlevel ACDF versus multilevel fusion for cervical disk disease involving 3 levels. *Orthopedics*. 2013;36(1):e88-e94.
38. Shin DA, Yi S, Yoon DH, Kim KN, Shin HC. Artificial disc replacement combined with fusion versus two-level fusion in cervical two-level disc disease. *Spine (Phila Pa 1976)*. 2009;34(11):1153-1159.
39. Wu TK, Wang BY, Deng MD, et al. A comparison of anterior cervical discectomy and fusion combined with cervical disc arthroplasty and cervical disc arthroplasty for the treatment of skip-level cervical degenerative disc disease: A retrospective study. *Medicine (Baltimore)*. 2017;96(41):e8112.
40. Xiong Y, Yang YD, Yu X, et al. Comparison of 2-year follow-up results of the hybrid surgery using Mobi-C combined with ROI-C and anterior cervical discectomy and fusion for the treatment of contiguous two-level cervical degenerative disc diseases. *J Clin Neurosci*. 2020;73:42-47.