Comparative Analysis of ABM/P-15, Bone Morphogenic Protein and Demineralized Bone Matrix after Instrumented Lumbar Interbody Fusion

Ashwin Sathe,1 Sang-Ho Lee,1 Shin-Jae Kim,1 Sang Soo Eun,2 Yong Soo Choi,1 Shih-min Lee,1 Ju-Wan Seuk,1 Yoon Sun Lee,1 Sang-Ha Shin,1 Junseok Bae1

Department of Neurological Surgery,1 Wooridul Spine Hospital, Seoul, Korea
Department of Orthopedic Surgery,2 Wooridul Spine Hospital, Seoul, Korea

Objective : ABM/P-15 (anorganic bone matrix/15-amino acid peptide fragment) is a commercially available synthetically manufactured P-15 collagen peptide fragment, that is adsorbed on ABM. This study was done to investigate the efficacy of ABM/P-15 in achieving fusion in the lumbar spine and comparing it with that of recombinant bone morphogenic protein-2 (rhBMP-2) and demineralized bone matrix (DBM).

Methods : A retrospective observational study of prospectively collected data of 140 patients who underwent lumbar spinal fusion surgeries in a single specialty spine hospital between 2016 and 2020, with a minimum 6-month follow-up was conducted. Based on the material used for the augmentation of the bone graft at the fusion site, the patients were divided into three categories namely ABM/P-15, rhBMP-2, and DBM group.

Results : ABM/P-15, rhBMP-2, and DBM were used in 46, 44, and 50 patients, respectively. Patient characteristics like age, gender, bone mineral density, smoking history, and presence of diabetes mellitus were comparable amongst the three groups. Average follow-up was 16.0±5.2, 17.9±9.8, and 26.2±14.9 months, respectively in ABM/P-15, rhBMP-2, and DBM groups. The fusion was achieved in 97.9%, 93.2%, and 98% patients while the average time-to-union was 4.05±2.01, 10±4.28, and 9.44±3.49 months (p<0.001), respectively for ABM/P-15, rhBMP-2, and DBM groups. The average pre-operative Visual analogue scale score was 6.93±2.42, 7.14±1.97, 7.01±2.14 (p=0.900) for ABM/P-15, rhBMP-2 and DBM groups, which reduced to 1.02±0.80, 1.21±0.96, and 0.54±0.70 (p=0.112), respectively at the last follow up. Pre-operative Oswestry disability index scores were 52.7±18.02, 55.4±16.8, and 53.56±19.6 (p=0.751) in ABM/P-15, rhBMP-2, and DBM groups, which post-operatively reduced to 33.77±15.52, 39.42±16.47, and 38.3±15.89 (p=0.412) and further to 15.74±8.3, 17.41±10.45, and 16.76±9.81 (p=0.603), respectively at the last follow-up.

Conclusion : ABM/P-15 appears to achieve union significantly earlier than rhBMP-2 and DBM in lumbar spinal fusion cases while maintaining a comparable clinical and complication profile.

Key Words : Lumbar vertebrae · Spinal fusion · Demineralized bone matrix · rhBMP-2 · Anorganic bone matrix/15-amino acid peptide fragment.
INTRODUCTION

The iliac crest autograft has long been considered as a gold standard in achieving surgical spinal fusion. However, the numerous disadvantages such as graft site morbidity, increased operative time, increased blood loss, risk of neurovascular injury, increased duration of hospital stay and cosmetic concerns are associated with autologous iliac crest grafting. Apart from this, the fact remains that the supply of iliac crest bone graft in a patient is finite and may not be sufficient in every case. Thus, there has been a constant quest to find substitutes to autologous bone grafting.

Allografts, demineralized bone matrix (DBM), ceramics and recombinant bone morphogenic protein-2 (rhBMP-2) are some of the substitutes that have been investigated to replace autografts for achieving interbody fusion, with varying success rates. The ABM/P-15 (anorganic bone matrix/15-amino acid peptide fragment) is a synthetically manufactured P-15 collagen peptide fragment, that is adsorbed on ABM and suspended in an inert hydrogel. This P-15 imitates the cell-binding domain of type one collagen and triggers biomechanical signals which ultimately result in new bone formation.

The use of ABM/P-15 has been well established in single level anterior cervical fusion surgeries. However, in the cases of lumbar fusion surgeries, more evidence is needed to establish its efficiency and safety. To address this lacuna in current scientific evidence, we compared ABM/P-15 with other commonly used bone graft substitute materials in lumbar interbody fusion surgeries namely rhBMP-2, and DBM in terms of their clinical and radiological outcomes as well as the side effect profile.

MATERIALS AND METHODS

Institutional Review Board (IRB) of Wooridul Spine Hospital approval was taken for this study (IRB No. 2021/04/WSH/002). A retrospective analysis of prospectively collected data of 140 patients with degenerative lumbar spinal pathologies, who underwent instrumented lumbar interbody fusion surgeries in a single specialty spine centre between the years 2016 and 2020 was conducted. The indications for surgery were lumbar degenerative disorders with instability/spondylolisthesis wherein fusion was deemed necessary. All patients with a minimum follow-up of 6 months were included. Patients with inadequate follow-ups, missed timely follow-ups, inadequate documentation of the records were excluded. Patients with concomitant posterior decompression at the index level, traumatic pathologies, infections, inflammatory or autoimmune diseases and tumours were excluded. The patients were operated either using anterior lumbar interbody fusion (ALIF), or oblique lumbar interbody fusion (OLIF)/direct lateral lumbar interbody fusion (DLIF) approach followed by percutaneous posterior pedicle screw fixation. The patients were divided into three groups based on the bone graft substitute used, namely ABM/P-15, rhBMP-2, and DBM group. The use of biologic grafts was applied consecutively according to the time of surgery; DBM was used from the year 2016 to August 2017, BMP was used from September 2017 to August 2019, and ABM/P-15 was used for surgery after September 2019. Following are the specifications and doses of the substitutes used: 1) rhBMP-2 (Novosis; CGBio, Seoul, Korea): rhBMP-2 + HA carrier (0.5 mg/level) mixed with allograft bone, 2) ABM/P-15 (i-Factor; Cerapedics, Westminster, CO, USA): 1 mL/level mixed with allograft, and 3) DBM (Grafton Orthoblend; Medtronic, Memphis, TN, USA): 5 mL/level (allograft mixed formula).

Commercially available cancellous allograft bone derived from the femoral head was used.

Clinical evaluation

All the patients were evaluated pre-operatively as well as in post-operative follow-up period using 10-point Visual analogue scale (VAS) for back pain and leg pain, and Oswestry disability index (ODI) was calculated in each of the patients. The incidences of complication such as infection, hematoma, wound complication, implant failure as well as unplanned revision and readmission were also noted.

Radiological evaluation

The patients underwent full-length, 36-inch exposure radiographs of the spine that extended from the base of the skull to the proximal femur in the antero-posterior and lateral planes pre-operatively, post-operatively in first week and on regular follow-up visits of 3, 6, 9, and 12 months postoperatively. All radiographs were obtained with the patients standing and looking forward trying to maintain a horizontal gaze and with their arms flexed, hands placed on their clavicles.
without any support, and knees extended. Radiological parameters such as pelvic incidence, sacral slope, lumbar lordosis, segmental Cobb’s angle, sagittal vertical axis, and cage subsidence were calculated in each radiograph using a program that included a built-in picture-archiving communication system (PiView; INFINITT Co. Ltd, Seoul, Korea). Lumbar dynamic radiographs were taken at each follow-up visit while computed tomography (CT) scan was done at 3-month and 12-month follow-up visit. This is done as an institutional protocol in our hospital as more frequent CT scans (which although have more diagnostic accuracy for detecting fusion) may result in radiation hazard to the patient. Thus, the interbody fusion was assessed on CT reconstruction images and/or flexion-extension lateral radiographs at the abovementioned follow-up intervals. Bone fusion was defined as solid when there was osseous continuity observed in CT reconstruction images and mobility of less than 4° on as seen in flexion-extension lateral radiographs. Nonunion was defined as the presence of a visible gap and mobility greater than 4°19).

Statistical analysis
The three groups were analysed for various clinical and radiological parameters using two-way analysis of variance (ANOVA), one-way ANOVA, chi-square test/fisher exact test. A subgroup analysis of rhBMP-2 and ABM/P-15 was also done to compare these two modalities. A p-value of <0.05 was considered as statistically significant. All analyses were performed using SPSS 14.0K (SPSS Inc., Chicago, IL, USA).

RESULTS
Overall, 401 patients (116 ABM/P-15, 108 rhBMP-2, and 177 DBM) were identified to have undergone anterior or lateral lumbar interbody fusion surgery between the study time period. After applying the inclusion criteria, 140 patients were enrolled for the study. Out of 140 patients, ABM/P-15, rhBMP-2, and DBM were used in 46, 44, and 50 patients, respectively.

Table 1. Various characteristics of the study population

| Patient characteristic | ABM/P-15 (n=46) | rhBMP-2 (n=44) | DBM (n=50) | p-value |
|------------------------|-----------------|----------------|------------|---------|
| Age (years)            | 67.3±7.9        | 68.8±7.1       | 65.5±7.9   | 0.091   |
| Male (%)               | 15.2            | 14.0           | 20.0       | 0.074   |
| BMD                    | -2.26±1.32      | -2.14±1.03     | -1.89±0.99 | 0.257   |
| BMI                    | 24.9±3.5        | 25.2±3.8       | 25.1±3.5   | 0.940   |
| Diabetics (%)          | 23.9            | 23.3           | 32.0       | 0.955   |
| Smokers (%)            | 2.2             | 0.0            | 3.3        | 0.760   |
| Follow-up (months)     | 16.0±5.2        | 17.9±9.8       | 26.2±14.9  | 0.001   |
| Surgery                |                 |                | 0.001      |         |
| ALIF                   | 40 (87.0)       | 23 (51.1)      | 42 (84.0)  |         |
| LLIF                   | 6 (13.0)        | 21 (48.9)      | 8 (16.0)   |         |

Values are presented as mean±standard deviation or number (%). ABM/P-15 : anorganic bone matrix/15-amino acid peptide fragment, rhBMP-2 : recombinant bone morphogenic protein-2, DBM : demineralized bone matrix, BMD : bone mineral density, BMI : body mass index, ALIF : anterior lumbar interbody fusion, LLIF : lateral lumbar interbody fusion

Table 2. Characteristics of the achievement of union in ABM/P-15, rhBMP-2 and DBM groups

|                  | ABM/P-15 | rhBMP-2 | DBM   | p-value |
|------------------|----------|---------|-------|---------|
| Union achievement (months) | 4.05±2.01 | 10.00±4.28 | 9.44±3.49 | <0.001 |
| 3–6              | 41 (89.1) | 13 (29.4) | 12 (24.0) |         |
| 7–12             | 4 (8.7)   | 24 (54.5) | 33 (66.0) |         |
| >13              | 0 (0.0)   | 4 (9.0)   | 4 (8.0)   |         |
| Avg. time to union (months) | 0.05±0.01 | 0.00±0.00 | 0.00±0.00 | >0.001  |
| Non union        | 1 (2.1)   | 3 (6.8)   | 1 (2.0)   | 0.429   |
| Union            | 24 (52.2) | 14 (32.6) | 28 (56.0) | 0.429   |
| Probable union   | 21 (45.7) | 27 (60.6) | 21 (42.0) | 0.429   |

Values are presented as mean±standard deviation or number (%). ABM/P-15 : anorganic bone matrix/15-amino acid peptide fragment, rhBMP-2 : recombinant bone morphogenic protein-2, DBM : demineralized bone matrix, Avg. : average

Fig. 1. Box plot showing the number of patients achieving union. There is a clear time advantage for the ABM/P-15 group as compared to rhBMP-2 and DBM group. ABM/P-15 : anorganic bone matrix/15-amino acid peptide fragment, rhBMP-2 : recombinant bone morphogenic protein-2, DBM : demineralized bone matrix.
Average age of the entire study population was 67.15 years with 88.43% female patients. Patient characteristics like age, gender, bone mineral density smoking history and presence of diabetes mellitus were comparable amongst three groups (Table 1).

Average follow-up was 16.0±5.2, 17.9±9.8, and 26.2±14.9 months.
months, respectively in ABM/P-15, rhBMP-2, and DBM groups. The average time to union was 4.05±2.01, 10.00±4.28, and 9.44±3.49 months, respectively for ABM/P-15, rhBMP-2, and DBM groups (p<0.001) (Fig. 1). At the last follow-up, fusion was achieved 97.9%, 93.2%, and 98% in ABM/P-15, rh-BMP-2, and DBM groups, respectively. Eighty-nine percent patients treated using ABM/P-15 showed fusion within first 6 months (Table 2 and Figs. 2-4).

The average pre-operative back VAS score was 6.93±2.42, 7.14±1.97, 7.01±2.14 (p=0.900), respectively, which reduced to 1.02±0.80, 1.21±0.96, and 0.54±0.70 (p=0.112) at the last follow-up. The pre-operative ODI scores were 52.70±18.02, 55.39±16.80, and 53.56±19.61 (p=0.751), which in the post-operative period reduced to 33.77±15.52, 39.42±16.47, and 38.30±15.89 (p=0.412), respectively and to 15.74±8.30, 17.41±10.45, and 16.76±9.81 (p=0.603), respectively at the last follow-up (Table 3).

There were no incidences of infection in ABM/P-15 and rhBMP-2 group while three patients in DBM group were infected. One patient in each rhBMP-2 and ABM/P-15 group, while two patients in DBM group suffered superficial wound complications. The incidence of cage subsidence was 21.7%, 30.2%, and 14%, respectively in ABM/P-15, rh-BMP-2, and DBM group (p=0.332). Most of this subsidence was grade 1 (76.9%) while 15.4% of the subsidence was grade 2 (80%) of the subsidence in ABM/P-15 group, 72% in rh-BMP-2 group, and

| Table 3. Clinical characteristics of all the three groups at different time intervals |
|---------------------------------|----------------|----------------|----------------|----------------|
| Back VAS score                  | ABM/P-15  | rhBMP-2 | DBM | p-value |
| Preop                           | 6.93±2.42 | 7.14±1.97 | 7.01±2.14 | 0.900 |
| Immediate postop                | 2.85±1.47 | 3.28±1.35 | 2.90±1.85 | 0.782 |
| Last F/U                        | 1.02±0.80 | 1.21±0.96 | 0.54±0.70 | 0.112 |
| LEG VAS score                   | ABM/P-15  | rhBMP-2 | DBM | p-value |
| Preop                           | 6.23±2.58 | 6.93±2.75 | 6.36±2.33 | 0.398 |
| Immediate postop                | 2.93±1.74 | 3.42±1.62 | 3.02±2.16 | 0.589 |
| Last F/U                        | 1.04±0.98 | 1.21±0.96 | 0.89±1.06 | 0.183 |
| ODI                             | ABM/P-15  | rhBMP-2 | DBM | p-value |
| Preop                           | 52.70±18.02 | 55.39±16.80 | 53.56±19.61 | 0.751 |
| Immediate postop                | 33.77±15.52 | 39.42±16.47 | 38.30±15.89 | 0.412 |
| Last F/U                        | 15.74±8.30 | 17.41±10.45 | 16.76±9.81 | 0.603 |

Values are presented as mean±standard deviation. ABM/P-15 : anorganic bone matrix/15-amino acid peptide fragment, rhBMP-2 : recombinant bone morphogenetic protein-2, DBM : demineralized bone matrix, VAS : Visual analogue scale, preop : preoperative, postop : postoperative, F/U : follow-up, ODI : Oswestry disability index.

Fig. 4. Case presentation of a 60-year-old female patient who underwent anterior lumbar interbody fusion with percutaneous pedicle screw fixation at the L3-4 and L4-5 level using DBM mixed with allograft. Postoperative lateral radiographs on 3-month (A), 9-month (B), and sagittal reconstructed computed tomography scan on 9-month (C) showing union was achieved on 9-month follow-up. DBM : demineralized bone matrix.
85.7% in DBM group was grade 1 subsidence).

**DISCUSSION**

Lumbar interbody fusions are one of the commonest spine surgeries performed in the world and the incidence of this procedure is rising steadily. Achieving predictable and rapid fusion is necessary for a successful outcome in these patients. The use of bone graft substitutes has been prompted by the numerous disadvantages in the use of autologous iliac crest bone graft, most notably post-operative pain at the donor site. There has been a constant effort to develop an ideal bone graft substitute which would possess all the three properties of an autologous bone graft, namely osteogenesis, osteoinduction, and osteoconduction. However, none of the synthetically derived materials have shown to possess all the three properties. Nevertheless, many of these substances have shown clinical usefulness in achieving fusion. In this study we compared three commonly used bone graft substitutes, which have gathered attention in recent years, namely ABM/P-15, rhBMP-2, and DBM.

DBM, which is created by demineralization of human cadaveric bones using acid, has osteoinductive as well as osteoconductive properties and has shown fusion rates of approximately 90%. DBM contains multitudes of proteins such as low molecular weight BMPs, collagen and some non-collagenous materials which have pivotal roles in bone formation.

rhBMP-2 has a higher osteoinductive as well as osteoconductive properties than DBM, however it has shown varying fusion rates ranging from 40–100%. Another point of concern with rhBMP-2 has been the risk of heterotrophic ossification, osteolysis, subsidence, inflammation and neoplasm. It has been reported that the actual rate of complications after the use of rhBMP-2 is 10 to 50 times higher than what has been reported by the industry sponsored clinical trials. In our study, we could not find evidence of ectopic bone formation or neoplastic change in any of the three groups.

The earlier evidences and consequently the clinical use of ABM/P-15 was established in various orthopaedic as well as dental surgeries where the ABM/P-15 was used in the treatments of long bone non-unions as well as in gingival recession of defects and periodontal defects. Extrapolating the successful experience from these subspecialities, the use of ABM/P-15 was investigated in spinal surgery.

Arnold et al. conducted a randomised controlled trial to investigate the non-inferiority of ABM/P-15 bone graft as compared to autologous bone graft in single level cervical fusion surgery for cervical radiculopathy. ABM/P-15 and autograft group showed 88.97% and 85.82%, fusion rates respectively at the end of 1-year follow up. They concluded that ABM/P-15 meets the noninferiority success criteria as per the FDA requirements and it was safe as well as effective in single-level anterior cervical interbody fusion in cases of cervical radiculopathy.

There are very few studies in the literature investigating lumbar spinal fusion using ABM/P-15. In a study by Lauwers and Raskin, the efficacy and safety of ABM/P-15 in 40 patients treated with posterior lumbar interbody fusion was analysed. In their study they inserted two cages at each level to be fused. One cage was filled with autologous graft while the other was filled with ABM/P-15. They found that the evidence of intra cage bone bridging at 6 months was seen in >97% cages with ABM/P-15 and, 59% cages with autologous graft. Mobb et al. studied the clinical outcomes and fusion rates after ALIF surgeries using ABM/P-15, and found that at a mean 2 years follow up, fusion was seen in 97.5%, 81%, and 100% of patients, who underwent single, double, and triple-level fusion surgeries respectively.

On the other hand, Jacobsen et al. conducted a randomised controlled trial comparing the fusion rates in elderly Scandinavian population treated with non-instrumented ALIF using allografts and ABM/P-15. They found that at 1 year post surgery, the rate of fusion in the ABM/P-15 group was 50% while that in the allograft group was 20%. All the patients in this study were elderly with osteoporosis and no instrumentation was used for fixing the spinal segments. Since rigid fixation and stability provided by the instrumentation has an important mechanical role in preventing instability and movement at the spinal segment, not using any instrumentation may be responsible for the relatively lower rates of fusion reported in this study.

In our study the rate of fusion in the ABM/P-15 group was 97.9%, with 89.1% patients showing radiological evidence of fusion within 6-month post-surgery. The average time to union of 4.05 months in ABM/P-15 group which was significantly lower than the other two (10 months and 9.44 months respectively for rhBMP-2 and DBM group). Apart from this,
there was no significant difference between the health-related quality of life (HRQoL) parameters measured by the ODI scores among the three groups. This highlights the efficiency of ABM/P-15 in achieving rapid fusion while achieving comparable HRQoL outcomes.

Cage subsidence was the most common complication in our study. We had as 30.2% subsidence rate in rhBMP-2 group followed by ABM/P-15 group and DBM group with 21.7% and 14% subsidence rate. However, this difference was not statistically significant when compared between all the three groups. As per the classification proposed by Sharma et al.30 most of these patients had grade 1 subsidence. The effect of subsidence on the overall clinical outcome was not unfavourable as suggested by the back and leg VAS scores and ODI scores. This was expected, as low-grade subsidence is considered an expected outcome, rather than a surgical complication21,22. The incidence of deep infection was 6% in DBM group, with no patients infected in ABM/P-15 and rhBMP-2 group. The superficial wound complications were seen in one patient each in rhBMP-2 and ABM/P-15 group and in two patients in DBM group.

Heterotrophic ossification has been reported as one of the side effects of using ABM/P-15 as described in a case report of an 8-year-old patient with mucopolysaccharidosis treated with spinal fusion using ABM/P-1528. However, in our study we could not find evidence of heterotrophic ossification in any patient. This also has a bearing with surgical technique, wherein, it is advised not to perform saline irrigation of the wound once the cage with ABM/P-15 is inserted as it can lead to localised deposition of ABM/P-15 along with the irrigation fluid which may stimulate ossification at ectopic sites. In addition to this, the authors seal the cage using either oxidized regenerated cellulose (Surgicel®; Johnson and Johnson Medical, Arlington, TX, USA) or a water-soluble bone hemostatic agent (Ostene, Baxter, CA, USA) to prevent the ABM/P-15 from flowing out of the cage.

Our study is unique in many aspects. In this study, we have compared three types of bone graft substitutes namely ABM/P-15, rhBMP-2, and DBM and have compared their clinical and radiological outcomes as well as complication profile. Apart from this, the study also encompasses cases treated with ALIF, OLIF, and DLIF approaches, followed by percutaneous pedicle screw fixation which have recently gathered more attention as minimally invasive fusion approaches17,20,26,32. Limitations of our study include the retrospective design and shorter follow-up. Thus, some of the complications like the heterotrophic ossification may not become apparent in the short-term follow-up. As the bone graft substitutes were used serially over a period of 5 years it may be possible that the experience of the providing surgeon(s) increased which may theoretically improve patient selection, risk mitigation, and surgical technical skill, which can impact the outcomes. At present, a prospective randomised controlled double blinded multicentric trial is planned to obtain high quality, level one evidence to further investigate the efficacy as well as cost effectiveness of ABM/P-15 in lumbar spinal fusion.

**CONCLUSION**

ABM/P-15 appears to achieve union in lumbar fusion cases significantly earlier than rhBMP-2 and DBM, while maintaining favorable clinical and complication profile. Further prospective long term clinical trials comparing different bone graft substitutes with emphasis on the cost analysis should be undertaken to further build on the currently available evidence.

**AUTHORS’ DECLARATION**

**Conflicts of interest**

No potential conflict of interest relevant to this article was reported.

**Informed consent**

Informed consent was obtained from all individual participants included in this study.

**Author contributions**

Conceptualization : JB; Data curation : SJK, SSE, YSC, YSL, SHS, JB; Formal analysis : SJK, YSL; Methodology : JB; Project administration : JB; Visualization : SL, JWS; Writing - original draft : AS; Writing - review & editing : SHL, JB

**Data sharing**

None
References

1. Arnold PM, Sasso RC, Janssen ME, Fehlings MG, Heary RF, Vaccaro AR, et al. : i-Factor™ bone graft vs autograft in anterior cervical discectomy and fusion: 2-year follow-up of the randomized single-blinded food and drug administration investigational device exemption study. Clin Neurosurg 83 : 377-384, 2018

2. Arnold PM, Sasso RC, Janssen ME, Fehlings MG, Smucker JD, Vaccaro AR, et al. : Efficacy of i-Factor bone graft versus autograft in anterior cervical discectomy and fusion: results of the prospective, randomized, single-blinded Food and Drug Administration investigational device exemption study. Spine (Phila Pa 1976) 41 : 1075-1083, 2016

3. Bae J, Lee SH : Minimally invasive spinal surgery for adult spinal deformity. Neurosurgery 15 : 18-24, 2018

4. Banwart JC, Asher MA, Hassanien RS : Iliac crest bone graft harvest donor site morbidity. A statistical evaluation. Spine (Phila Pa 1976) 20 : 1055-1060, 1995

5. Barros RR, Novaes AB Jr, Roriz VM, Oliveira RR, Grisi MF, Souza SL, et al. : Anorganic bovine matrix/P-15 “flow” in the treatment of periodontal defects: case series with 12 months of follow-up. J Periodontol 77 : 1280-1287, 2006

6. Bhatnagar RS, Qian JJ, Gough CA : The role in cell binding of a beta-bend within the triple helical region in collagen alpha 1 (I) chain: structural and biological evidence for conformational tautomerism on fiber surface. J Biomol Struct Dyn 14 : 547-560, 1997

7. Carragee EJ, Hurwitz EL, Weiner BK : A critical review of recombinant human bone morphogenetic protein-2 trials in spinal surgery: emerging safety concerns and lessons learned. Spine J 11 : 471-491, 2011

8. Chung HJ, Hur JW, Ryu KS, Kim JS, Seong JH : Surgical outcomes of anterior cervical fusion using deminalarized bone matrix as stand-alone graft material: single arm, pilot study. Korean J Spine 13 : 114-119, 2016

9. Cook RW, Hsu WK : Ceramics: clinical evidence for ceramics in spine fusion. Semin Spine Surg 28 : 217-225, 2016

10. Gomar F, Orozco R, Villar JL, Arrizabalaga F : P-15 small peptide bone graft substitute in the treatment of non-unions and delayed union. A pilot clinical trial. Int Orthop 31 : 93-99, 2007

11. Gupta A, Bukhar N, Sharif K, Main BJ, Albers CE, El-Amin II SF : Bone graft substitutes for spine fusion: a brief review. World J Orthop 6 : 449-456, 2015

12. Hanks T, Atkinson BL : Comparison of cell viability on anorganic bone matrix with or without P-15 cell binding peptide. Biomaterials 25 : 4831-4836, 2004

13. Haws BE, Khechen B, Patel DV, Yoo JS, Guntin JA, Cardinal KL, et al. : Impact of iliac crest bone grafting on postoperative outcomes and complication rates following minimally invasive transforaminal lumbar interbody fusion. Neurospine 16 : 772-779, 2019

14. Jacobsen MK, Andresen AK, Jepsersen AB, Stattrup C, Carreón LY, Overgaard S, et al. : Randomized double blind clinical trial of ABM/P-15 versus allograft in noninstrumented lumbar fusion surgery. Spine J 20 : 677-684, 2020

15. Katsoura Y, Shafi K, Jacques C, Vird S, Iyer S, Cunningham M : New strategies in enhancing spinal fusion. HSS J 16 : 177-182, 2020

16. Kukreja S, Ahmed OI, Haydel J, Nanda A, Sin AH : Complications of anterior cervical fusion using a low-dose recombinant human bone morphogenetic protein-2. Korean J Spine 12 : 68-74, 2015

17. Kyoh Y : Minimally invasive endoscopic-assisted lateral lumbar interbody fusion: technical report and preliminary results. Neurospine 16 : 72-81, 2019

18. Lauweryns P, Raskin Y : Prospective analysis of a new bone graft in lumbar interbody fusion: results of a 2-year prospective clinical and radiological study. Int J Spine Surg 9 : 2, 2015

19. Lee DY, Jung TG, Lee SH : Single-level instrumented mini-open transforaminal lumbar interbody fusion in elderly patients. J Neurosurg Spine 9 : 137-144, 2008

20. Lim TK, Lee SG, Park CW, Kim WK, Son S, Lee K : Comparative analysis of adjacent levels of degeneration and clinical outcomes between conventional pedicle screws and percutaneous pedicle screws in treatment of degenerative disease at L3-5: a preliminary report. Korean J Spine 9 : 66-73, 2012

21. Marchi L, Abdala N, Oliveira L, Amaral R, Coutinho E, Pimenta L : Radiographic and clinical evaluation of cage subsidence after stand-alone lateral interbody fusion. J Neurosurg Spine 19 : 110-118, 2013

22. Martin BI, Mirza SK, Spina N, Spiker WR, Lawrence B, Brodke DS : Trends in lumbar fusion procedure rates and associated hospital costs for degenerative spinal diseases in the United States, 2004 to 2015. Spine (Phila Pa 1976) 44 : 369-376, 2019

23. Melisel HJ, Agarwal N : Commentary on "biomaterials in spinal implants: a review". Neurosurgery 17 : 111-113, 2020

24. Mobbs RJ, Chung M, Rao P : Bone graft substitutes for anterior lumbar interbody fusion. Orthop Surg 5 : 77-85, 2013
25. Mobbs RJ, Maharaj M, Rao PJ: Clinical outcomes and fusion rates following anterior lumbar interbody fusion with bone graft substitute i-FACTOR, an anorganic bone matrix/P-15 composite. *J Neurosurg Spine* **21**: 867-876, 2014

27. Na YC, Lee HS, Shin DA, Ha Y, Kim KN, Yoon DH: Initial clinical outcomes of minimally invasive lateral lumbar interbody fusion in degenerative lumbar disease: a preliminary report on the experience of a single institution with 30 cases. *Korean J Spine* **9**: 187-192, 2012

27. Nazareth CA, Cury PR: Use of anorganic bovine-derived hydroxyapatite matrix/cell-binding peptide (P-15) in the treatment isolated class I gingival recession of defects: a pilot study. *J Periodontol* **82**: 700-707, 2011

28. Oxborrow N, Sundarapandian R: Heterotopic ossification following use of i-Factor for spinal fusion in mucopolysaccharidosis I: a case report. *J Surg Case Rep* 2018: rjy120, 2018

29. Sasso RC, LeHuec JC, Shaffrey C: Iliac crest bone graft donor site pain after anterior lumbar interbody fusion: a prospective patient satisfaction outcome assessment. *J Spinal Disord Tech* **18**: S77-S81, 2005

30. Sharma AK, Kepler CK, Girardi FP, Cammisa FP, Huang RC, Sama AA: Lateral lumbar interbody fusion: clinical and radiographic outcomes at 1 year: a preliminary report. *J Spinal Disord Tech* **24**: 242-250, 2011

31. Vaccaro AR, Chiba K, Heller JG, Patel TCh, Thalgott JS, Truumees E, et al.: Bone grafting alternatives in spinal surgery. *Spine J* **2**: 206-215, 2002

32. Xi Z, Chou D, Mummaneni PV, Burch S: The navigated oblique lumbar interbody fusion: accuracy rate, effect on surgical time, and complications. *Neurospine* **17**: 260-267, 2020