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Efficacy of Biocage in treating single-segment lumbar degenerative disease in patients with high risk of non-fusion: a prospective controlled study with at least 2 years' follow-up

Yang Li[1,*], Yang Yu[2,*], Tian-yong Hou[1], Ze-hua Zhang[1], Jun-chao Xing[1], Hong-wei Lu[1], Rui Zhou[1], Peng Cheng[1], Jian-Zhong Xu[1], Wen-jie Wu[1,#] and Fei Luo[1,#]

Abstract

Objective: To evaluate the clinical efficacy of an allogeneic bone cage (Biocage; Beijing Datsing Bio-Tech Co., Ltd., Beijing, China) for treatment of single-segment lumbar degenerative disease in patients with a high risk of non-fusion.

Methods: From January 2013 to December 2016, 67 patients who underwent lumbar fusion were divided into the Biocage group (n = 33) and polyether ether ketone (PEEK) group (n = 34). The patients were followed up for 24 to 48 months. The mean intervertebral height of the fusion level, fusion rate, height of the intervertebral foramen, visual analog scale score, and Oswestry disability index were compared.

[1]National & Regional Engineering Laboratory of Tissue Engineering, Department of Orthopedics, The First Affiliated Hospital to Army Medical University (Southwest Hospital), Chongqing, China
[2]Department of Orthopedics, Hospital of Chengdu University of Traditional Chinese Medicine, Chengdu, China

[*]These authors contributed equally to this work and should be considered co-first authors.

[#]These authors contributed equally to this work and should be considered co-authors.

Corresponding author:
Fei Luo, National & Regional Engineering Laboratory of Tissue Engineering, Department of Orthopedics, The First Affiliated Hospital to Army Medical University (Southwest Hospital), 30 Gao Tan-yan Street, Sha Ping-ba District, Chongqing 400038, China.
Email: luofeispine@126.com

Results: The PEEK group had a lower fusion rate than the Biocage group (88.24% vs. 90.91%), although the difference was not statistically significant. During follow-up, the height of the intervertebral space was similar between the Biocage and PEEK groups (12.88 ± 0.45 and 12.84 ± 1.01 mm, respectively). The height of the intervertebral foramen was larger in the Biocage than PEEK group (20.67 ± 1.34 vs. 20.00 ± 2.05 mm). Good clinical efficacy was achieved in both groups.

Conclusion: The Biocage is efficient and safe for treatment of single-segment lumbar degenerative disease in patients with a high risk of non-fusion.

Keywords

Allogeneic bone, cage, polyether ether ketone, lumbar interbody fusion, high-risk, lumbar degenerative disease

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Introduction

Since the pioneering efforts made by Albee[1] and Hibbs and Peltier[2] in the early 20th century, there have been great changes in spinal fusion techniques. During the last century, autologous bone grafting has enhanced the direct bone formation required for successful spinal fusion. However, the incidence of pseudarthrosis is still as high as 26%.[3] Despite the use of modern bone grafting techniques and advanced internal fixation devices, symptomatic pseudarthrosis still occurs in 10% to 15% of patients.[4–6] Factors associated with a high risk of non-fusion after spinal fusion include old age, smoking, and osteoporosis. The underlying cause of these risk factors is a decline in osteogenesis. Therefore, in theory, promoting patients' osteogenic ability can increase the rate of spinal fusion.

Allogeneic bone has been widely applied during the past three decades and has many advantages in the clinical setting, especially with respect to promoting osteogenesis. Its efficacy as bone graft material is thought to be second only to autologous bone. The allogeneic bone cage Biocage (Beijing Datsing Bio-Tech Co., Ltd., Beijing, China) was designed and developed based on previous research and is made of allogeneic cortical bone with inexpensive materials and high bone grafting ability. The Biocage has good biocompatibility and minimal stress shielding.[7] It also exhibits bone-inductive and bone-conductive effects, benefitting fusion. Both sides of the Biocage are designed according to the anatomical shape of the lumbar vertebrae. The endplate has a large contact area, which facilitates a uniform load distribution and avoids endplate cutting. The upper and lower endplates have dentate protrusions, which can effectively prevent cage slippage and promote stabilization immediately after the operation. Additionally, the Biocage has a sagittal convex angle of 12 degrees, which is designed to restore the physiological curvature of the lumbar spine. The Biocage allows for postoperative observation of the fusion through X-ray examination. It was designed as a single instrument that is placed diagonally in the intervertebral space and is suitable for most intervertebral fusion procedures.

Polyether ether ketone (PEEK) is an engineering plastic and is the most widely used intervertebral fusion device in the clinical setting. However, PEEK is a polymer

material that does not possess the three-dimensional mesh structure required for osteogenesis and is therefore not conducive to the replacement of bone by creeping substitution. Moreover, as a foreign body within the intervertebral space, it occupies the space needed for fusion of normal bone tissues. In theory, it will inevitably affect the firmness of fusion. Therefore, PEEK is not the perfect material with which to make a cage.

Few studies have compared the Biocage and PEEK cage in patients with a high risk of non-fusion. Therefore, we performed a prospective study in which we examined the clinical efficacy of the Biocage and PEEK cage in patients with a high risk of non-fusion to provide reference information for cage selection in intervertebral fusion for such patients.

Materials and methods

Biocage

We used the Biocage, a contoured, wedge-shaped cortical allograft biological cage (Figure 1) with a central bone planting window and a side hole with a diameter of 2 mm in accordance with the characteristics of the human body. The surface of the spacer contained a saw-tooth pattern on the superior and inferior surfaces to minimize migration, and the purpose of the side hole was generation of new bone and blood vessels. Donor cortical femur bone was used to fabricate the cage. A dovetail slot structure was used to assemble two cortical bone pieces into one cage. In addition to the mounting mechanisms, 4-mm anterior and posterior allograft bone screws were used to assemble the two cortical bone pieces (Figure 2).

Study design

In this prospective, parallel-control study, the patients were divided into the experimental group (Biocage group) and the control group (PEEK group). The patients in the Biocage group were treated with the allograft fusion device (Biocage), and the patients in the PEEK group were treated with an intervertebral fusion device made of PEEK material (Medos International Sàrl, Le Locle, Neuchâtel, Switzerland). All patients were followed up to evaluate the preoperative, intraoperative, and postoperative clinical indicators and thus determine the clinical efficacy of the Biocage.

Figure 1. Biocage.

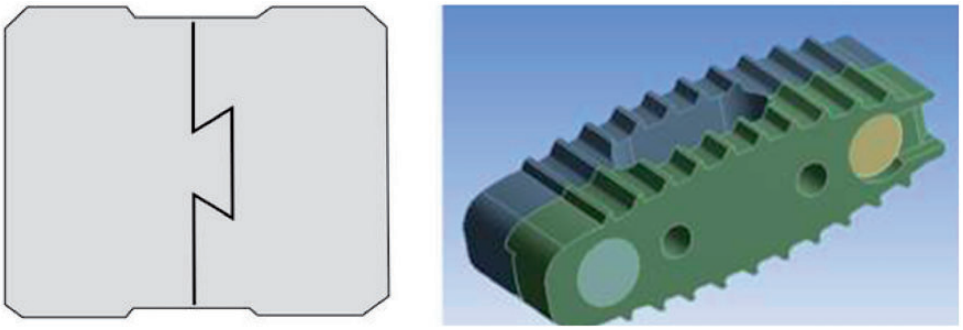

Figure 2. Two- and three-dimensional views of the mounting mechanism of the Biocage.

The following non-inferiority test formula was used to estimate the sample size: $N = 2 \times (U_{\alpha} + U_{\beta})2 \times P(1 - P)/\delta 2$, where N indicates the sample size, $\alpha = 0.05$, $\beta = 0.02$, δ (non-inferiority margin) = 10%, and P was set to 98% as the 1-year postoperative spinal fusion rate. This formula resulted in $N = 25$. Considering the possibility of patient loss, a minimum of 35 patients was required for each group.

Inclusion criteria. All patients included in the study had been diagnosed with single-level lumbar degenerative disease and had high-risk factors for non-fusion, including an age of >60 years and at least one of the following conditions: osteoporosis (T-score of <-2.5), smoking of >20 cigarettes/day for >5 years, or diabetes. All patients had lumbar degenerative disease manifesting as paralysis, weakness of the lower extremities, pain in the waist and lower extremities, or obvious instability of the lumbar vertebrae along with a weakened tendon reflex. Additionally, the patients had experienced no relief of their symptoms after >3 months of conservative treatment. No patients had contraindications for treatment.

Exclusion criteria. The exclusion criteria were an age of ≤60 years; intervertebral infection; reoperation for lumbar degenerative disease; multi-segment lumbar degenerative disease; fracture at the surgical site; congenital malformations; tumors; mental, endocrine, metabolic, or neurological disease; and severe lung, heart, kidney, or liver disease.

Patient enrollment process. All patients were required to meet the inclusion criteria, and those who met the exclusion criteria were not enrolled. The patients were informed of the relevant information of this study in detail. Eligible patients were enrolled after they had provided written informed consent. They were allowed to choose the type of fusion device (Biocage or PEEK cage) and were then assigned to the corresponding research group.

Evaluation indexes. The operation time, bleeding volume, and hospitalization duration were recorded. The visual analog scale (VAS) score was assessed before the operation and at 1 week and 3 months after the operation. The Oswestry disability index (ODI) score was evaluated before the operation and at 6 and 12 months after the operation. Fusion was identified as follows: trabecular bone passed through the endplates, the displacement of the adjacent vertebral body was <3 mm in hyperflexion and hyperextension, and the displacement of adjacent endplates was <5° in over flexion and extension. The fusion rate, height of the

intervertebral foramen, intervertebral space height, and complications were also compared between the groups.

Operation methods. The patients underwent general anesthesia in the prone position. A posterior midline incision was made through the conventional lumbar posterior approach. The vertebral plate and articular process were exposed, and four pedicle screws were implanted. The upper and lower laminae and the articular process on one side were resected to expose the dural sac and nerve roots. The nerve roots were then protected, the intervertebral disc was removed through the intervertebral space, and the upper and lower vertebral cartilage was removed with a circular curette. The excised autologous bone was implanted into the intervertebral space, and a suitable cage was filled with the autologous bone and inserted into the intervertebral space. Rods were placed and the screws were tightened. Antibiotics were administered to prevent infection for 2 to 3 days after the operation. Several patients underwent drainage tube placement. At 4 or 5 days postoperatively, the patients began to walk under protection with a brace.

Statistical analysis

Data are expressed as mean ± standard deviation. SPSS version 20.0 software (IBM Corp., Armonk, NY, USA) was used for the statistical analysis. An independent-samples t test was used to compare measurement data between the two groups, such as the VAS score, ODI score, operation time, bleeding volume, and hospitalization duration. The χ^2 test was used to compare enumeration data. A P value of <0.05 was considered statistically significant.

Ethics statement

This study was approved by the Medical Ethics Committee of the First Affiliated Hospital to Army Medical University [LYP No. 2013 (1)]. Written informed consent was obtained from all patients or their legal representatives.

Results

Patients' general characteristics

From January 2013 to December 2016, 70 patients were enrolled in this study and divided into the Biocage group (n = 35) and PEEK group (n = 35). The patients' medical history was collected, and all patients underwent preoperative neurological examinations, lumbar anteroposterior and lateral dynamic X-ray examinations, and computed tomography/magnetic resonance imaging examinations. Three patients were lost to follow-up (two in the Biocage group and one in the PEEK group). In the Biocage group, 14 patients had lumbar spondylolisthesis, 15 patients had lumbar disc herniation, and 4 patients had lumbar spinal stenosis. In the PEEK group, 14 patients had lumbar spondylolisthesis, 11 patients had lumbar disc herniation, 7 patients had lumbar spinal stenosis, and 2 patients had degenerative lumbar scoliosis. The patients' general characteristics are shown in Table 1.

Delayed incision healing occurred in one patient in each group. The patients were followed up for 24 to 48 months (mean of 30 months). There were no statistically significant differences in the general characteristics of the patients between the two groups, such as age, sex, fused levels, and risk factors (Table 1).

Perioperative results

As shown in Table 2, the operation time, bleeding volume, and hospitalization

duration were not significantly different between the two groups.

Pain and functional recovery

The preoperative and postoperative VAS score and ODI score are shown in Table 3. The VAS score and ODI were not significantly different between the groups. In both groups, the patients' symptoms and functional recovery were significantly improved after the operation ($P < 0.05$).

Imaging follow-up results

Although the fusion rate was higher in the Biocage group than in the PEEK group, the difference was not statistically significant (Table 4). During follow-up, there was no significant difference in the height of the intervertebral space or the height of the intervertebral foramen between the two groups (Tables 5, 6; Figures 3, 4).

Complications

No intraoperative complications were reported in either group. Delayed incision healing was found in one patient in each group, and no incision infection or leakage of cerebrospinal fluid occurred in any patients. At the last follow-up, non-fusion was present in three patients in the Biocage group and four patients in the PEEK group. None of them needed revision. The incidence rate of non-fusion was not significantly different between the two groups.

Discussion

The objective of lumbar interbody fusion is to stabilize the motion segment and promote bone fusion.[8,9] Compared with interlaminar and interspinous bone grafting, interbody fusion can provide support for the anterior and middle columns. The fusion of the bone graft is accelerated and easily distinguished on X-ray images.[10,11] Although the overall understanding of lumbar intervertebral bone grafting has been unified, controversy still exists in the selection of bone grafting materials.[12,13] Autologous bone is characterized by fresh material, strong osteoinductive activity, no immune rejection, elasticity closest to the human physiological state, and low cost. However, the bone source limitation, donor pain, bleeding, and risk of infection

Table 1. Baseline characteristics.

Characteristics	Biocage (n = 33)	PEEK cage (n = 34)	P value
Sex			
Male	15	15	0.912
Female	18	19	
Age, years	67.61 ± 4.93	66.30 ± 5.09	0.746
Fused level			
L1–L2	0	1	0.986*
L2–L3	1	1	
L3–L4	1	1	
L4–L5	21	21	
L5–S1	10	10	
Risk factors			
Osteoporosis	10	17	0.100
Smoking	16	14	0.548
Diabetes	9	4	0.109

Data are presented as n or mean ± standard deviation.
*In the chi-square test, patients with L1–L5 fusion were merged and compared with patients with L5–S1 fusion.

Table 2. Perioperative results.

Group	Biocage	PEEK cage	P value
Operation time, minutes	182.61 ± 42.95	191.15 ± 38.18	0.702
Amount of bleeding, mL	358.19 ± 248.10	392.65 ± 189.15	0.164
Hospitalization duration, days	14.42 ± 10.27	11.15 ± 4.68	0.140

Data are presented as mean ± standard deviation.

Table 3. VAS and ODI scores.

Time	Pre-op	7 days post-op	3 months post-op	6 months post-op	12 months post-op	24 monthspost-op	Final follow-up
Biocage							
VAS	5.70 ± 0.95	2.42 ± 0.50	2.09 ± 0.38	1.67 ± 0.54	1.27 ± 0.57	1.36 ± 0.49	1.27 ± 0.57
ODI	48.36 ± 8.73			30.67 ± 5.51	23.15 ± 5.33	25.96 ± 6.23	23.15 ± 5.33
PEEK							
VAS	5.65 ± 1.12	2.09 ± 0.38	1.91 ± 0.45	1.88 ± 0.54	1.44 ± 0.50	1.38 ± 0.55	1.44 ± 0.50
ODI	50.97 ± 6.84			29.47 ± 5.60	25.47 ± 5.08	29.03 ± 5.11	25.47 ± 5.08
P value							
P1	0.34	0.38	0.57	0.12	0.87	0.49	0.87
P2	0.14			0.75	0.49	0.40	0.48

Data are presented as mean ± standard deviation.
VAS, visual analog scale; ODI, Oswestry disability index; pre-op, preoperatively; post-op, postoperatively.

constrain its application.[4,14] In contrast, the sources of allogeneic bone are unlimited. Moreover, allogeneic bone effectively avoids donor site complications, exhibits osteoinductivity and osteoconductivity, and provides a biological environment that benefits bone growth. Thus, allogeneic bone is considered a promising alternative to autologous bone.[15,16] With the development of processing technology, the deficiencies of allograft bone have been improved. Few studies to date have focused on the application of allogeneic bone in lumbar fusion for patients with a high risk of non-fusion. Therefore, the present study was designed to observe the fusion of a new allogeneic bone cage (Biocage) in these patients and compare its safety and effectiveness with those of the PEEK cage.

Scarce literature currently exists on this topic. Arnold et al.[17] used parallel allograft cages to treat lumbar degenerative disease in 72 patients who were followed up for 2 years, and the 1-year fusion rate was 98%. Cutler et al.[18] compared the effects of allogeneic femoral rings and PEEK cages in patients undergoing transforaminal lumbar interbody fusion, and the fusion rate was 95.2% and 100%, respectively. There was no difference in maintenance of lumbar lordosis between the two groups.[18] In another study, the early clinical results of an allogeneic tibia loop were significantly better than those of a PEEK cage.[19] In the present study, there was no significant difference in the fusion rate between the two groups, although the PEEK group showed better performance. Olivares-Navarrete et al.[20] performed an *in vitro* study showing that the osteogenic maturity of the PEEK surface-forming phenotype was significantly lower than that of the metal cage surface, suggesting that the PEEK cage could only provide less intervertebral fusion. The reason for the decline in the PEEK fusion rate was considered to be related to inertia.[20] As a polymer material, PEEK does

Table 4. Fusion rate of Biocage and PEEK cage at 2-year follow-up.

Group	Osteoporosis	Smoking	Diabetes	Overall
Biocage	10/8 (80.00%)	16/15 (93.75%)	9/9 (100.00%)	33/30 (90.91%)
PEEK cage	17/15 (88.24%)	14/12 (85.71%)	4/4 (100.00%)	34/30 (88.24%)
P value	0.613	0.586	–	0.721

Data are presented as total/fused (fusion rate).

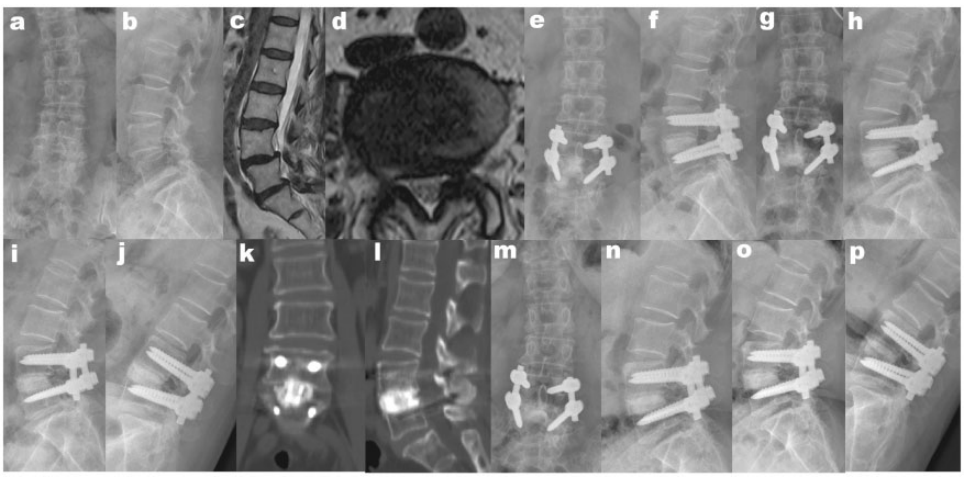

Figure 3. Representative case in which the Biocage was used for transforaminal lumbar interbody fusion. The patient was a 70-year-old woman with lumbar spondylolisthesis, osteoporosis, and hypothyroidism. (a–d) Preoperative lateral X-ray images and magnetic resonance images. (e, f) X-ray images 7 days after the operation. (g–l) X-ray images and computed tomography images 3 months after the operation. (m–p) X-ray images 34 months after the operation.

not have the desired three-dimensional network structure conducive to creeping substitution of bone. In the present study, there was a difference in the maintenance of intervertebral fusion between the two groups. In terms of the height of the intervertebral space, Liljenqvist et al.[21] reported that in patients who underwent lumbar interbody fusion with allogeneic femoral condyles, the fusion rate reached 95.2% during an 8.7-month follow-up. However, the height of the intervertebral space was different at 12 months, declining by 3 mm compared with that before the operation. Cutler et al.[18] also reported that the intervertebral height was more effectively maintained with a PEEK cage than with an allogeneic femoral ring. In contrast to previous reports, the present study showed that the height of the intervertebral space and the height of the intervertebral foramen were maintained in both of the groups. We believe that the Biocage maintained the intervertebral height and relative intervertebral height for two main reasons. First, two main autogenous or allograft bones were used for structural support: a femoral/fibular ring and three cortical bones. Both of them were obtained by a simple process after which the autogenous or allograft bone shapes did not match the endplate, resulting in stress concentration, endplate

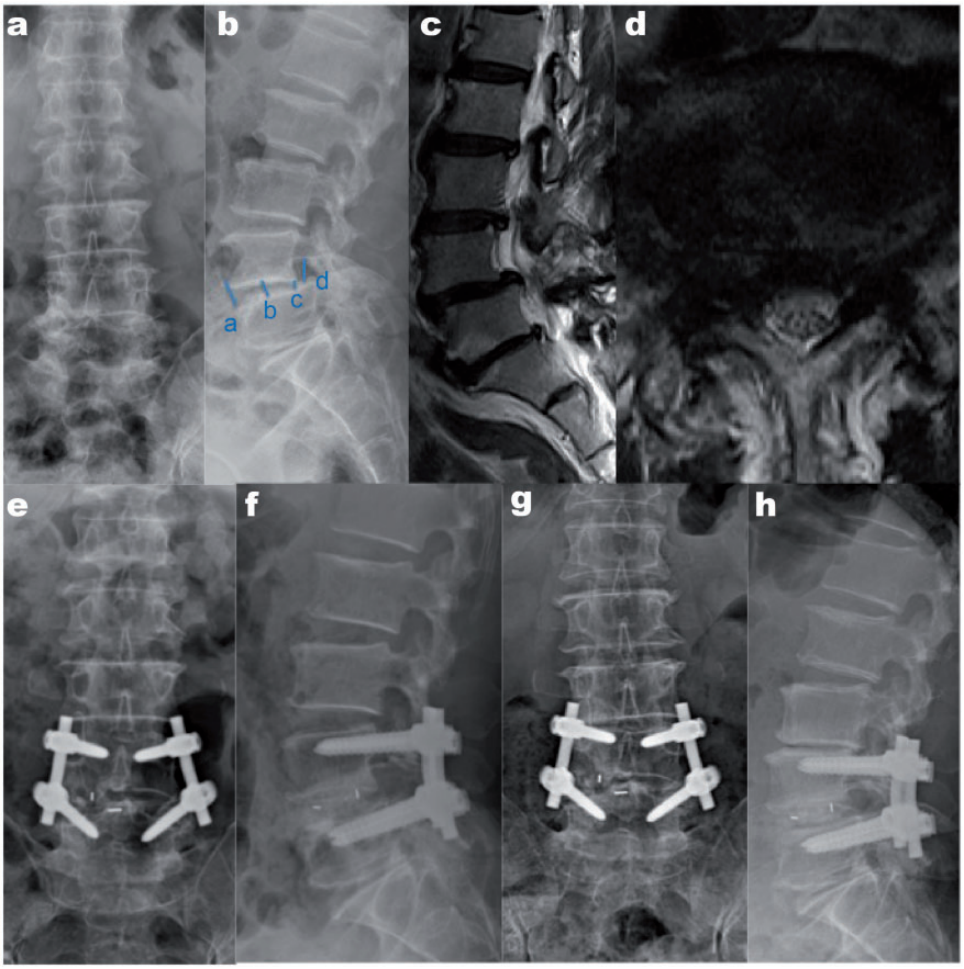

Figure 4. Representative case in which PEEK cage was used for transforaminal lumbar interbody fusion. The patient was a 72-year-old man with lumbar spondylolisthesis and diabetes. (a–d) Preoperative lateral X-ray images and magnetic resonance images. The mean intervertebral height of the fusion segment ([a + b + c]/3) is shown in (b), and the height of the intervertebral foramen is shown in (d). (e, f) X-ray images 7 days after the operation. (g, h) X-ray image 31 months after the operation.

Table 5. Mean intervertebral space height (mm).

Group	Pre-op	7 days post-op	Final follow-up
Biocage	10.83 ± 1.32	13.15 ± 1.28	12.88 ± 0.45
PEEK cage	10.68 ± 1.04	13.51 ± 1.59	12.84 ± 1.01
P value	0.60	0.32	0.86

Data are presented as mean ± standard deviation.
pre-op, preoperatively; post-op, postoperatively.

Table 6. Intervertebral foramen height (mm).

Group	Pre-op	7 days Post-op	Final follow-up
Biocage	16.11 ± 2.08	21.47 ± 1.79	20.67 ± 1.34
PEEK cage	15.74 ± 1.92	22.31 ± 2.11	20.00 ± 2.05
P value	0.46	0.83	0.12

Data are presented as mean ± standard deviation.
pre-op, preoperatively; post-op, postoperatively.

cutting, and loss of intervertebral height. Furthermore, the center of the three cortical bones was cancellous bone, and the mechanical strength was insufficient. The Biocage adopted the splicing method to match the curvature of the endplate, which helped to reduce the stress concentration. Second, the shape of the Biocage was similar to that of the PEEK cage, helping to disperse stress and prevent slippage. Cortical bone might provide sufficient mechanical strength to support the spine. Moreover, the Biocage could be absorbed.

The literature contains few reports on lumbar fusion in patients with a high risk of non-fusion. Okuyama et al.[22] analyzed 52 patients who underwent posterior lumbar interbody fusion and found that the bone density was significantly correlated with the success rate of fusion. The authors stated that osteoporosis was an important risk factor for non-fusion. Several studies have demonstrated that intervertebral collapse, delayed healing, and non-fusion are more common in patients of advanced age than in younger patients, and the main reason may be related to osteoporosis.[23–25] In the present study, 27 patients had osteoporosis (10 in the Biocage group and 17 in the PEEK group). At the 2-year follow-up, two patients with osteoporosis in each group had pseudarthrosis, which might have been related to the osteoporosis. In addition, smoking can reportedly affect bone fusion.[26] In a recent clinical study, Phan et al.[27] found that after anterior lumbar interbody fusion, the fusion rate was significantly lower in smokers than in nonsmokers. Nicotine is the main ingredient in tobacco, and large doses of nicotine can inhibit the proliferation of osteoblasts and increase the expression of osteocalcin and type I collagen. Iwaniec et al.[28] found that in mice that were administered nicotine, the blood phosphorus level increased, parathyroid hormone level increased, and calcitonin level decreased. These changes might weaken bone formation and affect spinal fusion. In the present study, 30 patients had a severe smoking habit (20 cigarettes/day) and 3 patients exhibited failed fusion at the 24-month follow-up. At the last follow-up, only the marginal portions of the cage were fused. In another unpublished study by our research team, smoking <10 cigarettes/day yielded no significant delay or non-fusion. The reason might be that nicotine has a dose-related effect on spinal fusion. The mechanism by which high-dose nicotine reduces spinal fusion might be explained as follows. 1) Nicotine interferes with serum calcium, phosphorus, and parathyroid hormone and affects calcitonin metabolism. 2) Nicotine acts on blood vessels around the bone graft area, thus affecting the formation of new capillaries, reducing the blood supply to the bone graft area, and hindering the formation of new bone. 3) Nicotine might block the proliferation and differentiation of osteoblasts, thereby reducing the speed of spinal fusion. In the present study, 13 patients were diagnosed with diabetes before the operation, but no patients had non-fusion at the

2-year follow-up. In many studies, however, the non-healing rate of lumbar fusion was higher in patients with than without diabetes. The reason is that the excessive blood glucose concentration in patients with diabetes leads to osteoblast and osteoclast dysfunction, causing postoperative non-fusion.[29–31]

This study was a preliminary exploration of the integration of high-risk factors for non-fusion. We believe that further subdivision analysis of the risk factors for fusion has important clinical significance. This study indicates that certain patient characteristics, such as smoking and osteoporosis, seem to increase the risk of non-fusion, pointing the way for further research. Notably, the follow-up time in this study was short. The contour of the Biocage could still be clearly seen at the last follow-up, suggesting that the allograft bone had not yet been fully absorbed. Long-term follow-up is needed to determine when the Biocage can be completely replaced. Additionally, the sample size was small. Although the sample was calculated based on the fusion rate, the spectrum of diseases and risk factors were not strictly distinguished. Further studies with larger sample sizes will be able to focus on specific diseases and risk factors.

Conclusion

The Biocage showed definite efficacy in lumbar fusion for patients with a high risk of non-fusion. The Biocage not only showed efficacy similar to that of the PEEK cage, but it also retained the advantages of allografts. Thus, the Biocage is worthy of popularization and application as a fusion material in lumbar fusion.

Author declaration

We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all authors. We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing we confirm that we have followed the regulations of our institutions concerning intellectual property. We further confirm that any aspect of the work covered in this manuscript that has involved human patients has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript. We understand that the corresponding author is the sole contact for the editorial process (including contact with the editorial manager and direct communications with the office). He is responsible for communicating with the other authors about the progress, submissions of revisions, and final approval of proofs. We confirm that we have provided a current, correct email address that is accessible by the corresponding author and that has been configured to accept email from luofeispine@126.com or bisheng320@126.com.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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ORCID iDs

Yang Yu https://orcid.org/0000-0002-6145-8811
Ze-hua Zhang https://orcid.org/0000-0002-4700-5111
Fei Luo https://orcid.org/0000-0002-6368-6674

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