

Clinical outcomes of treatment with cage-shaped demineralized bone plus local bone grafts vs. autogenous iliac crest bone grafts in instrumented single-level lumbar fusion: A retrospective cohort study

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Received April 16, 2019; Accepted October 3, 2019

DOI: 10.3892/etm.2019.8171

Abstract. The aim of the present study was to compare the clinical outcomes of cage-shaped demineralized bone plus local bone grafts (CDBLG) with those of autogenous iliac crest bone grafts (ICBG) implanted for the treatment of single-level lumbar intervertebral disc degenerative diseases. A total of 69 cases of degenerative spinal disorder treated between January 2011 and December 2013 were retrospectively analyzed. Of these, 44 were treated with CDBLG and 25 with autogenous ICBG. All fusions were instrumented single level. Fusion was assessed after 6, 12 and 24 months by X-ray and CT scans post-operatively. Clinical outcomes were determined during follow-up and assessments included the Oswestry Disability Index, Visual Analogue Scale for back and leg pain and the Short Form-36 general health survey physical component summary. The results indicated that the overall fusion rate at 24 months post-operatively was higher in the ICBG group compared with that in the CDBLG group, although not significantly ($P>0.05$). All other outcome measures were significantly improved in the two groups after the surgery ($P<0.05$), but no significant differences were observed between the two groups ($P>0.05$). Blood loss and mean duration of surgery in the CDBLG group were significantly lower compared

with those in the ICBG group ($P<0.05$). In conclusion, CDBLG achieved a similar fusion rate and clinical outcome as ICBG but was associated with significantly reduced blood loss and mean duration of surgery. In conclusion, the present study provided CDBLG bone graft as an alternative option for single-level fusion.

Introduction

Lumbar fusion has been employed in a variety of disorders, including degenerative intervertebral disc herniation, lumbar spondylolisthesis, lumbar tuberculosis and spine tumors. Lumbar fusion originally involved autologous bone grafting, usually from the iliac crest, into the intervertebral space without the use of any screws or cages. The utilization of autogenous bone graft was thought to be the most reliable method for achieving solid spinal fusion. In 1936, Mercer (1) used tricortical iliac crest autografts for anterior interbody fusions. At present, autologous cortico-cancellous bone grafts are still regarded as the gold standard for spinal fusion (2). However, lumbar spinal fusion using autografts is commonly associated with extended surgical time, hematoma, wound healing problems, pain lasting >6 months with sensory loss, infection and fracture at the donor site (3-5). Even after the introduction of spinal instrumentation, including interbody cages and transpedicular screws, which provide instant stability to aid fusion, the procedure was still commonly associated with complications, including instrumentation failure, kyphosis and pseudarthrosis (6,7). Therefore, it would be beneficial if a more reliable autogenous bone graft for clinical therapy were to be established. In this light, the present study reported on a newly developed cage-shaped demineralized bone plus local bone graft (CDBLG), in which an allograft and autograft are combined to improve the above-mentioned issues. A comparison of the clinical outcomes of autogenous iliac crest bone graft (ICBG) with CDBLG in single-level lumbar fusion was provided.

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Key words: iliac crest bone graft, cage-shaped demineralized bone graft and local bone, lumbar fusion, degenerative spine

Patients and methods

CDBLG design. A CDBLG (Chinese patent no. ZL2008301126534) was developed, in which a local autograft was inserted into hollow allogeneic bone (Fig. 1A-C). In the present study, the allogeneic bone was not a simple graft as in previous studies but it was demineralized and formed into a cage-like shape. The structure of the CDBLG was designed to be wide at the front and narrow at the back, in accordance with the physiological characteristics of the spine. In addition, the allogeneic bone had high strength and was of low cost to suit the requirements of patients in the poor region of western China.

Inclusion and exclusion criteria. In this retrospective study, the inclusion criteria were as follows: i) Patient age, 20-75 years at the time of treatment; ii) degenerative disc disease, discogenic back pain with/without leg pain documented on X-ray films, CT or MRI; iii) the patient is a candidate for only one-level posterolateral lumbar fusion; iv) unresponsive to conservative treatment for a period of 3 months and v) the patient signed an informed consent form specific to this study that was approved by the Review Board of the General Hospital of Xinjiang Military Region.

The following exclusion criteria were applied: i) Previous posterior lumbar fusion at the currently involved level; ii) presence of a hard- or soft-tissue infection at the operative site; iii) endocrine or metabolic disorder affecting osteogenesis (e.g., insulin-dependent diabetes, renal osteodystrophy); iv) use of medications known to affect the skeleton, including long-term use of glucocorticoid or non-steroidal anti-inflammatory drugs; v) mental disorders (e.g., Alzheimer's disease or a diagnosed mental disorder); vi) tobacco users refusing to stop smoking 6 weeks prior to surgery until 1 year after surgery; and vii) patients with other diseases that do not allow for surgery.

Subjects. Following approval from the Review Board of the General Hospital of Xinjiang Military Region (approval no. ZYLL-2018-23) and obtainment of informed consent from all patients in accordance with the Declaration of Helsinki, 78 adult patients who had consecutively undergone lumbar decompression with transpedicular screw instrumented posterolateral fusion between January 2011 and December 2013 were selected for the present study. After exclusion of 9 patients, the cohort comprised 43 male and 26 female patients with degenerative spinal disorders. Of these, 44 received CDBLG and 25 cases were subjected to ICBG. The mean age of the patients was 52.6 ± 9.6 years (range, 34-75 years). The minimum follow-up duration was 2 years and the mean follow-up duration was 53 months (range, 24-71 months). All cases were diagnosed based on clinical symptoms, plain radiographs, MRI and electrophysiology examination.

Graft surgery technique. Autogenous ICBG were made in a standard open fashion (8). Freeze-dried allogeneic cortical bone grafts from the Shanxi Aorui Bone Bank were used to construct cage-shaped demineralized bone. Local bone grafts were obtained from a decompression procedure of the spinous process and lamina. All attached soft tissues were removed and the mixed cage-shaped demineralized bone and local bone fragment graft were used in the spinal surgery.

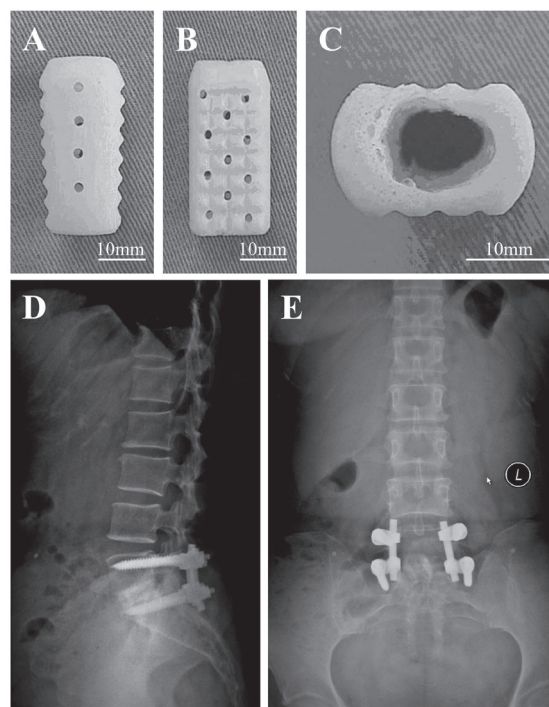


Figure 1. Hollow allogeneic bone and 24-month follow-up after interbody fusion of cage-shaped demineralized bone plus local bone graft. (A) Lateral view; (B) vertical view; (C) anterior view of the hollow allogeneic bone. (D) Antero-posterior X-ray and (E) lateral X-ray of the fusion graft (scale bar, 10 mm).

All patients underwent open posterior laminectomy, nerve decompression and pedicle screw instrumented single-level lumbar fusion, with patients placed in the prone position. After exposure of the vertebral laminae, nerve decompression was achieved by removal of the spinal process, vertebral lamina, attached ligamentum flavum and partial joint facet. The nucleus pulposus was then re-sectioned and the cartilage was removed from the endplates. A CDBLG or ICBG was then placed in the intervertebral space (Fig. 1D and E) and Horizon transpedicular screws (Medtronic Sofamor Danek) were placed in the target segments. The segments to be fused were joined using contoured rods (8).

Determination of fusion. The first method for the determination of fusion success was based on the Investigational Device Exemption protocol (9). According to this method, a fusion was considered successful when fulfilling the following standards: The presence of bilateral, continuous trabeculated bone connecting the transverse processes, translation of ≤ 3 mm and an angulation of $< 5^\circ$ on flexion/extension radiographs, and absence of cracking, as evidenced by radiolucent lines through the fusion mass. Furthermore, a second method based on CT scans was used. As reported by Williams *et al* (10), the presence of continuous bone connecting the vertebral bodies was considered to indicate successful fusion. Bone fusion usually is near completion at 6 months with evidence of bridging of the trabecular bone. The bridging bone is usually seen lateral to or within the implant. The radiographs and CT scans were evaluated by two independent radiologists who were blinded regarding the patient group 6, 12, and 24 months after surgery. A third adjudicate reviewer was used as required.

Table I. Demographics and characteristics of the patients.

Parameter	CDBLG (n=44)	ICBG (n=25)	P-value
Age (years)	53.2±10.8	51.7±11.5	0.589
Sex (male/female)	28/16	15/10	0.764
Body weight (kg)	70.4±9.8	68.6±11.1	0.487
Tobacco use	11	6	0.926
Alcohol use	13	8	0.831
Diabetes	2	1	1.000
Previous lumbar surgery	3	2	1.000
Level of fusion			1.000
L1-L2	0	0	
L2-L3	0	0	
L3-L4	6	3	
L4-L5	21	12	
L5-S1	17	10	

Values are expressed as the mean ± standard deviation or n. CDBLG, cage-shaped demineralized bone plus local bone grafts; ICBG, iliac crest bone grafts.

Clinical outcome assessments. Imaging analysis consisted of plain anteroposterior, lateral and flexion/extension radiographs, and fine-cut axial CT scans with sagittal and coronal reconstruction. These were performed pre-operatively and after 6, 12 and 24 months post-operatively.

Standard demographic data were collected for all patients, including age, sex, body weight, smoking and drinking history, diabetes and history of prior back surgery. Outcome measures consisting of Oswestry Disability Index (ODI) (11), Visual Analogue Scale (VAS) for back and leg pain (12), and Short Form-36 general health survey physical component summary (SF-36 PCS) (13) were collected pre-operatively and at 3, 6, 12 and 24 months post-operatively.

Statistical analysis. The data obtained from the 69 patients were compared using SPSS software (v20.0; IBM Corp.). The two groups were compared using the Wilcoxon rank-sum test for quantitative variables and Fisher's exact test for categorical variables. Outcomes were analyzed using a repeated-measures ANOVA with time as the factor within subjects and treatment as the factor between subjects. A post-hoc analysis using Bonferroni's adjustment was performed for further multiple comparisons. $P < 0.05$ was considered to indicate a statistically significant difference.

Results

Patient characteristics. Of the 78 patients initially included, 69 had complete data regarding outcome measures and radiographic assessments at 2 years. Diagnosis included degenerative lumbar herniated disc in 35 cases (51%, L1 to L5), lumbosacral herniated disc in 23 cases (33%, L5 to S1), degenerative lumbar or lumbosacral herniated disc with spondylolisthesis in 5 cases (7%) and degenerative scoliosis exceeding 20° in 6 cases (9%). The demographic data and disease characteristics of the patients, including age, sex, tobacco/alcohol use, diabetic

status and fusion level, are presented in Table I. There is no significant difference regarding all of the clinicopathological parameters between the two groups.

Radiologic outcomes. Solid fusion mass was observed at 24 months after L4-L5 fusion using CDBLG (Representative images in Fig. 2). Evaluation with the radiographic method indicated that 92.0% of patients in the ICBG group and 88.7% in the CDBLG group had evidence of interbody process fusion (Fig. 3). Thus, no significant differences between the ICBG and CDBLG groups were observed using the radiographic imaging and CT methods ($P > 0.05$).

Scoring. The ODI and VAS score for back and leg pain, as well as the SF-36 PCS significantly improved in the two groups post-operatively ($P < 0.05$). No significant differences between the CDBLG and ICBG groups were observed in the mean ODI score at 24 months ($P > 0.05$). At the pre-operative and various post-operative stages, no significant differences in ODI between the ICBG and CDBLG groups were detected ($P > 0.05$; Fig. 4A). In addition, no significant differences were observed between the ICBG and CDBLG groups in VAS score for back and leg pain, and in SF-36 PCS at any of the time-points ($P > 0.05$; Fig. 4B-D).

Surgical and clinical outcomes. Peri-operative parameters, including duration of surgery, blood loss and length of hospital stay are listed in Table II. The mean duration of surgery in the CDBLG group was significantly lower than that in the ICBG group (156 ± 25 vs. 198 ± 32 min; $P < 0.05$). Furthermore, the mean blood loss in the CDBLG group was significantly lower compared with that in the ICBG group (385 ± 35 vs. 589 ± 51 ml; $P < 0.05$). There was no significant difference between these two groups in the duration of hospital stay ($P > 0.05$). There were neither immunogenic complications nor immunosuppressive therapy after surgery.

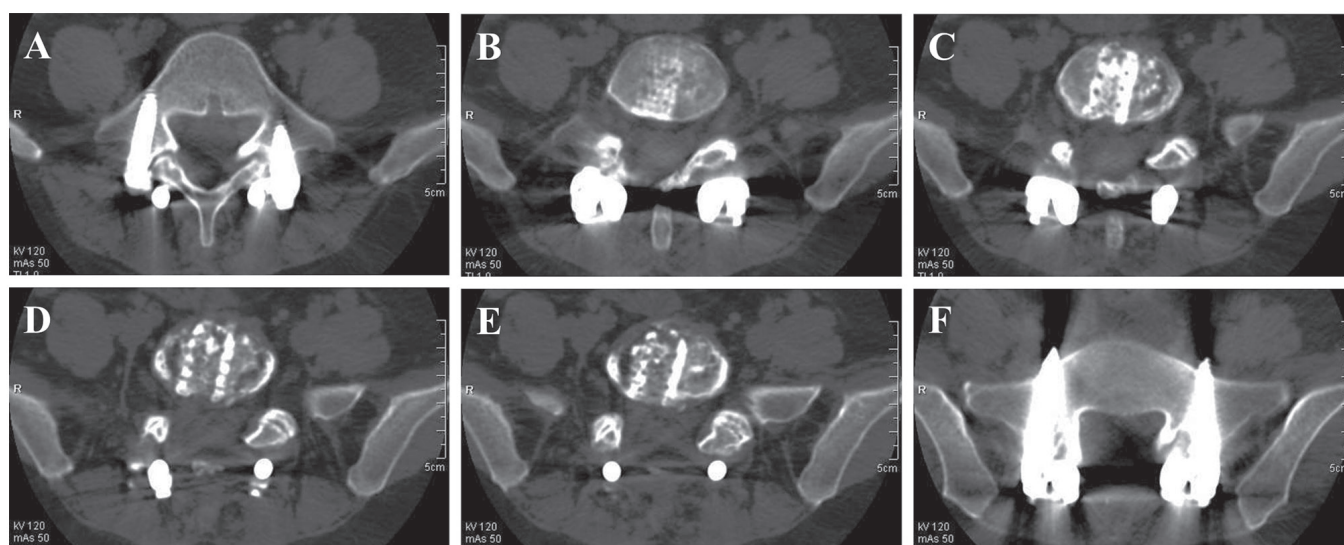


Figure 2. CT images from a representative patient of the cage-shaped demineralized bone plus local bone graft group 6 months after surgery. (A) The levels of upper transpedicular screw, (B) the level of endplate, (C and D) interbody fusion sites, (E) the level of the associated endplate, (F) the level of lower transpedicular screw.

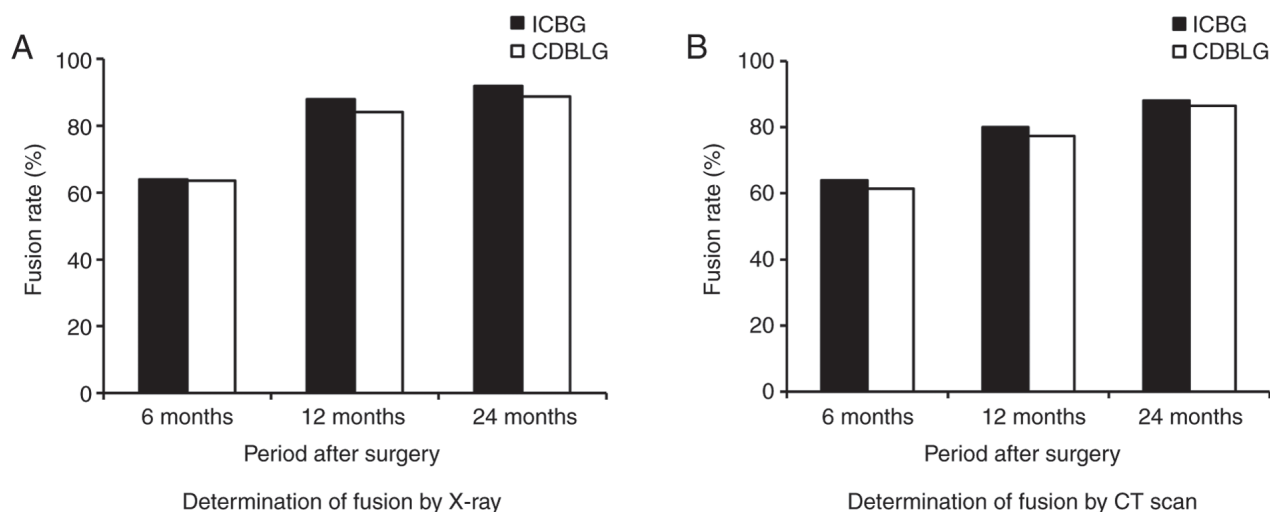


Figure 3. Fusion rates at 6, 12 and 24 months examined using (A) plain and flexion/extension X-ray radiographs and (B) CT scans. There was no statistically significant difference in the fusion rate between the CDBLG and ICBG group determined by the first or the second detection method [first detection method (plain and flexion/extension X-ray radiographs)], $P=0.918, 0.737$ and 0.967 at 6 months, 12 months and 24 months after surgery, respectively; second detection method (CT-scans), $P=0.818, 0.968$ and 1.000 in 6 months, 12 months and 24 months after surgery, respectively ($n=25$ in ICBG group and $n=44$ in CDBLG group). CDBLG, cage-shaped demineralized bone plus local bone grafts; ICBG, iliac crest bone grafts.

Discussion

Spinal surgery frequently requires bone grafts for fusion. Although numerous studies have reported successful fusion after instrumented interbody spinal fixation using autografts, fusion rates have large variances ranging from 40 to 98% were obtained (14-16). Autogenous ICBG remains the gold standard for spinal fusion; this material is easily available, and its use has no risk of transmitting disease and is effective in stimulating bone formation. Autogenous ICBG is the most common source of autografts. However, ICBG has various disadvantages, including limited resource of harvested bone and morbidity of the donor site, including infection, hematoma and sustained pain localized to the harvest site. Harvesting of autogenous ICBG also increases the duration of surgery, blood

loss and post-operative pain (17). The present study focused on comparing the efficacy of CDBLG and ICBG in single-level lumbar instrumented fusion. The cage-shaped demineralized bone graft provides a large surface where new bone formation occurs. Local autogenous bone includes osteoblasts and precursor cells, which respond to the local microenvironment, releasing stimulating factors that accelerate new bone formation and revascularization that has an important role in osteogenesis (18).

The cage-shaped demineralized bone graft provides mechanical stability, while local autogenous bone is rapidly incorporated into the surrounding lumbar vertebral bodies due to its osteogenic properties (19). The demineralized bone is composed of mineral and collagen, which serves as a scaffold to stimulate revascularization and to induce host precursor cells

Table II. Surgical and clinical information.

Characteristic	CDBLG (n=44)	ICBG (n=25)	P-value
Duration of surgery (min)	156±25	198±32	<0.001
Blood loss (ml)	385±35	589±51	<0.001
Hospital stay (days)	8.3±2.7	8.6±2.9	0.673

Values are expressed as the mean ± standard deviation. CDBLG, cage-shaped demineralized bone plus local bone grafts; ICBG, iliac crest bone grafts.

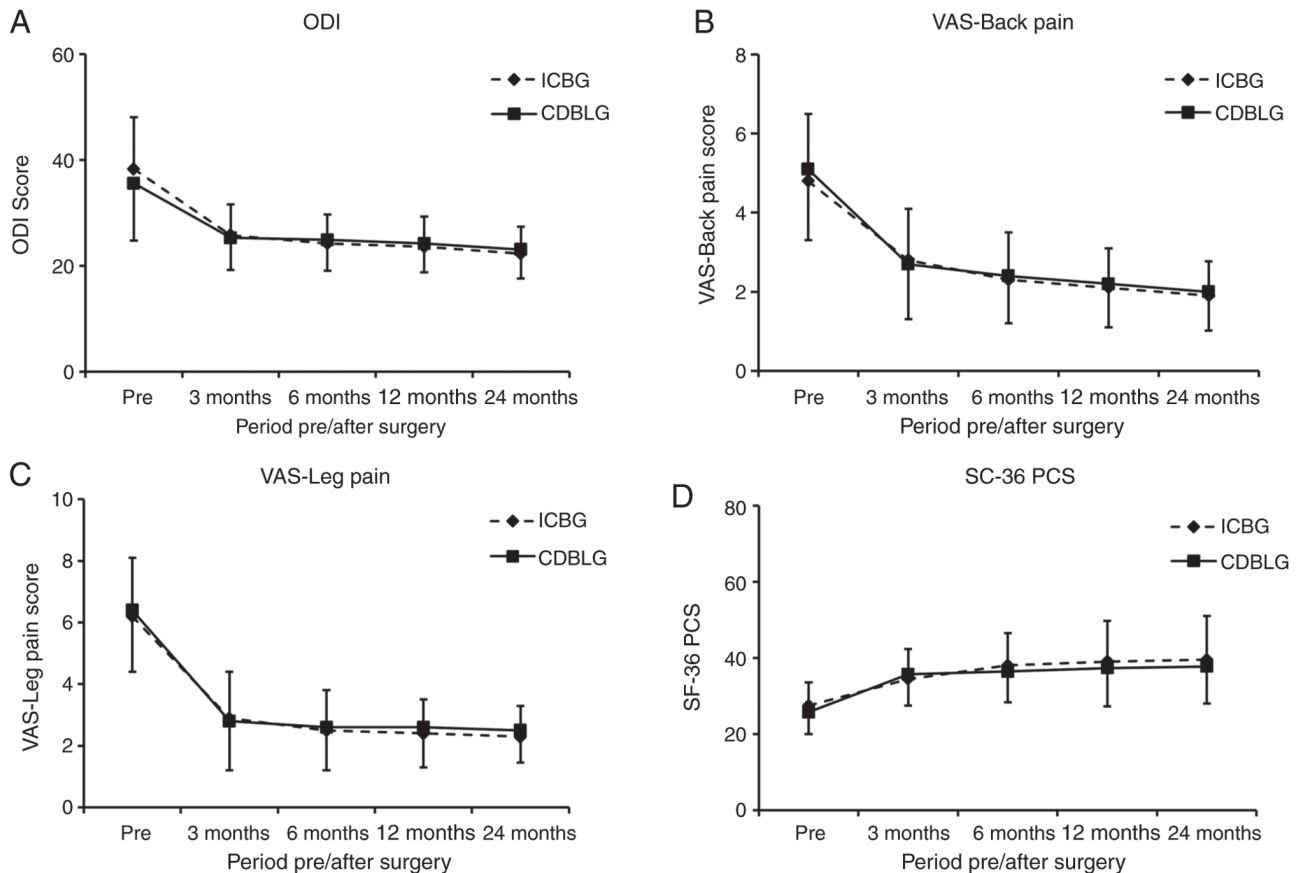


Figure 4. ODI, VAS and SF36-PCS for the CDBLG group and ICBG group. (A) ODI scoring; (B) VAS for back pain; (C) VAS for leg pain; (D) SF36-PCS scoring. There was no significant difference in ODI, VAS for back pain and leg pain, SF36-PCS scoring prior to or at 3, 6, 12 and 24 months after surgery between the CDBLG and ICBG groups ($P>0.05$; $n=25$ in ICBG group and $n=44$ in CDBLG group). CDBLG, cage-shaped demineralized bone plus local bone grafts; ICBG, iliac crest bone grafts; ODI, Oswestry Disability Index; VAS, Visual Analogue Scale; Pre, prior to surgery; SF36-PCS, Short Form-36 general health survey physical component summary.

to form new bone. Demineralized bone is usually derived from acid extraction of a human allograft, resulting in a combination of properties that are osteoconductive (organic matrix proteins) and osteoinductive (growth factors). Demineralized bone is acellular and less osteoconductive than autogenous bone, due to the acid extraction. The quantity and type of growth factors and cytokines influence the osteoinductive capacity of the demineralized bone graft (20). The extracellular matrix stimulates new bone formation via non-collagenous proteins and growth factors (21). Demineralized bone graft may be used as an effective bone graft substitute and may decrease morbidities associated with iliac bone graft harvest (22).

Flexion/extension radiographs, static radiographs, tomograms and the older generations of CT scans differ in their reliability and accuracy in determining the status of fusion, and therefore, discrepancies exist among previously published studies reporting on the rate of fusion (23-25). In the present study, progressive radiographic films were produced at 6, 12 and 24 months' follow-up to determine the progression and robustness of the interbody fusion mass. In the present study, the fusion rate at 24 months determined using plain and flexion/extension X-ray radiographs was 88.7% for CDBLG and 92.0% in ICBG (no significant difference, $P=0.967$), which is comparable to the results of previous studies that adopted

a similar methodology (14,26). The fusion rate based on CT scan evaluation and criteria in the CDBLG group was slightly, but insignificantly lower than that in the ICBG group (86.4 vs. 88.0%; $P=1.000$).

The osteogenic, osteoconductive and osteoinductive properties of CDBLG are similar to those of ICBG. However, the local bone in the CDBLG has no potential for histocompatibility and immunogenic reactions from allografts (4,9,27). The substantial morbidity associated with the procurement of autogenous bone has been a common complication, primarily due to the documented success of using autografts, in addition to the lack of commercially available bone graft substitutes that offer equal or superior rates of fusion (28,29). In their retrospective clinical study, Ito *et al* (30) reported that the fusion results and progression from the local bone group and the autologous iliac bone group were nearly identical.

In the present study, a novel type of bone graft, CDBLG, which had similar clinical outcomes to those of ICBG, was presented. The CDBLG was fabricated from osintegumentale, which has greater mechanical strength than autologous iliac bone. The CDBLG was effective in sustaining the height of the disc gap, better matching its natural physiological curvature, and as previously reported by Kang *et al* (31), it is therefore believed to be able to have comparable clinical outcomes to ICBG.

In the present study, a number of specific complications were observed in the ICBG group that may be attributed to the donor site. Blood loss and the duration of surgery were greater than in the CDBLG group. Allograft bone is available in large quantities but its osteogenic potential is markedly reduced compared with that of autografts, and it is associated with a risk of bacterial and viral infection (32,33). Overall, the successful fusion rate of CDBLG is comparable to that of an autogenous ICBG. As reported, Cage-shaped demineralized bone is an allograft from cadaveric bone without the mineral content which also has a low risk of disease transmission (34,35). The remaining type I collagen contains variable concentrations of growth factors and serves as an osteoconductive and osteoinductive scaffold that induces new bone formation (36). Demineralized bone was not used on its own for lumbar fusion. Combined with local autogenous bone harvested from elements of the posterior spinal structure, including the vertebral laminae, spinal processes and facet joint, it provides osteogenic cells that become incorporated into the surrounding vertebral bodies. Chen *et al* (37) reported that autologous laminectomy and spinal process bone achieved high fusion but posterolateral fusion required a greater quantity of bone. The cage-shaped demineralized bone graft was demonstrated to be a good bone graft extender. By combining with local bone, mainly from the spinal process and vertebral lamina, the CDBLG provides all three bone graft components for bone formation: Osteogenesis, osteoinduction and osteoconduction. Its use was reported to decrease the morbidities associated with autogenous iliac bone graft harvest for lumbar fusion and to also have a significantly reduced cost compared with the use of metal or polyetheretherketone (PEEK) intervertebral cages (38). Use of the CDBLG also decreased the duration of surgery and hospital stay compared with those of ICBG.

The present study had certain limitations. First, it was a retrospective study and the sample size was relatively small.

A randomized, controlled, prospective study should be performed to compare the clinical outcomes of CDBLG and ICBG. Furthermore, long-term follow-up should be performed. In addition, autogenous ICBG placement remains a good candidate for successful surgical treatment of spine instability. CDBLG was demonstrated to be a suitable alternative without problems of limited quantity and morbidity due to harvesting. Additional studies, including comparison of CDBLG with metal or PEEK interbody cage, should be performed.

In conclusion, treatment with CDBLG resulted in an equal rate of fusion and pain relief to that obtained with ICBG. All clinical outcome measures demonstrated significant improvement at all time-points of post-operative follow-up and there is no risk of rejection. Compared with ICBG, treatment with CDBLG was associated with significantly less intra-operative blood loss and a shorter duration of surgery. Therefore, the use of CDBLG bone graft is recommended as an alternative option for single-level fusion.

Acknowledgements

Not applicable.

Funding

The present study was supported by the Medical Research Program in 'Science and Technology +' projects of Xi'an city [grant no. 201805096YX4SF30(2)] and the Shaanxi Natural Science Basic Research Grant (grant no. 2018JQ8063). The funders had no role in the study design, data collection and analysis or decision to publish the manuscript.

Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

CGZ and JQ analyzed the data and wrote the manuscript. GX, YJ and YCG carried out the surgeries. XW carried out patient follow-up. XM and HY were the lead investigators, and developed the design of the study, analysis and interpretations. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This study has been approved by the Review Board of the General Hospital of Xinjiang Military Region (approval no. ZYLL-2018-23). Informed consent, in accordance with the Declaration of Helsinki, was obtained from all patients.

Patient consent for publication

The patients have provided consent for publication of CT images which appeared in the manuscript.

Competing interests

The authors declare that they have no competing interests.

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