Feasibility And Safety of A CaO-SiO2-P2O5-B2O3 Bioactive Glass Ceramic Spacer In Posterior Lumbar Interbody Fusion: A Prospective Randomized Controlled Trial

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Abstract

Study design: Prospective randomized controlled trial.

Background: The CaO-SiO2-P2O5-B2O3 glass-ceramic (BGS-7) spacer is a recently developed spacer that shows chemical bonding to bone with high mechanical stability. Further, this spacer achieves similar results to those of titanium cages. However, evidence regarding the advantages of the BGS-7 spacer is weak compared to polyetheretherketone (PEEK) cage. A randomized controlled trial is therefore warranted. The purpose of this study was to compare the radiographic and clinical efficacies and safety of the BGS-7 spacer compared to those of the PEEK cage in patients who underwent posterior lumbar interbody fusion (PLIF).

Methods: The 54 participants who required one- or two-level PLIF due to lumbar degenerative disorders were randomly assigned to receive a BGS-7 spacer or PEEK cage. Visual analog scale (VAS), Oswestry Disability Index (ODI), European Quality of Life-5 Dimensions (EQ-5D), painDETECT score were evaluated before surgery and at 3, 6, and 12 months after surgery. The fusion rate, degree of osteolysis, cage migration and subsidence around the cage (spacer) were evaluated on computer tomography (CT) images at 12 months after surgery.

Results: The 12-month fusion rates were 75% in the BGS-7 spacer group and 79.3% in the PEEK cage group, with no significant difference (p=0.676). The result regarding the non-inferiority of BGS-7 spacer was inconclusive. The linear mixed model showed no significant intervention effect in VAS, ODI, EQ-5D, and painDETECT score at the 3-, 6-, or 12-month follow-up. In addition, we found no significant between-group differences in the extent of osteolysis, spacer migration. However, the subsidence around the cage was significantly lower in the BGS-7 spacer group.

Conclusions: This trial found similar fusion rates, clinicoradiographic outcomes, and adverse events between the BGS-7 spacer and PEEK cage for PLIF. However, the non-inferiority was inconclusive, and thus, the BGS-7 spacer can be a feasible and safe alternative to PEEK cage in PLIF surgery after further studies.

Introduction

Posterior lumbar interbody fusion (PLIF) is one of the treatment options for patients with degenerative lumbar disease.[1, 2] The intervertebral cage or spacer used in PLIF restores the intervertebral height and relieves the patient’s symptoms.[3] For the intervertebral fusion, the gold standard material for intervertebral spacer is still a harvested auto-bone from the iliac crest as it has a high fusion rate, good biocompatibility, and non-immunogenicity. However, harvested auto-bones have the disadvantages of donor site pain, hematoma, infection, and fracture.[4, 5] As such, many alternative materials such as polyetheretherketone (PEEK) and titanium have been developed and are currently used more often over auto-bones. However, PEEK cages do not have the capability to bind to bone by itself, and thus, it has to

be filled with bone graft substitutes, such as autobone, allobone, or synthetic bone, which induce bone union.[5, 6]

Another recently developed material is bioactive glass ceramics that is known to chemically bind to bone, forming a carbohydroxy apatite layer.[7] Bioactive glass ceramics with better mechanical strength have been developed for bone graft and repair.[7, 8] Among the many types of bioactive glass ceramics, CaO-SiO_2-P_2O_5-B_2O_3 glass-ceramics (BGS-7) have been reported to induce osteoblastic differentiation of human mesenchymal stem cells, resulting in improved bone-implant contact ratio.[9] Furthermore, intravenous BGS-7 administration in rats did not show any toxicity for 90 days.[10] The compressive strength and bending strength of BGS-7 is also at least two times higher than that of hydroxyapatite.[11] Previous studies showed that BGS-7 spacers in PLIF achieve similar fusion rates, clinical outcomes, and adverse events to titanium cages at 1 and 4 years postoperative.[12, 13] BGS-7 spacers also achieved a larger area of fusion with the endplates than did titanium cages. However, to our best knowledge, there has been no comparative study between PEEK cages and BGS-7 spacers in PLIF surgery.

The purpose of our study was to assess the feasibility and safety of the BGS-7 spacer (Fig. 1) as an alternative to the PEEK cage in PLIF. Towards this goal, we recruited patients with lumbar degenerative spinal disease who required one- or two-level PLIF, and they were assigned to receive either a BGS-7 spacer or a PEEK cage filled with local auto bone during PLIF. The clinicoradiographic outcomes were then compared between the two groups.

Materials And Methods

Study design and participants

This prospective, randomized, non-inferiority clinical trial was approved by the institutional review board of our hospital (B-1708/412-004) and was conducted according to the tenets of the 1964 Helsinki Declaration and its later amendments. The trial was registered at ClinicalTrials.gov as NCT03302520. All participants provided written informed consent before enrollment.

The subjects were patients aged 30–80 years who required one- or two-level PLIF between L1 and S1. They were selected among those who required an extensive laminectomy or facetectomy to correct severe disc extrusion, severe spinal stenosis, or spondylolisthesis. The exclusion criteria were as follows: (1) severe osteoporosis (below − 3.5 T-score on bone densitometry at L1-4); (2) positive pregnancy test before the trial or who planned to become pregnant within the following 3 years; (3) a history of malignant tumor or malignant diseases (patients with cured disease with no relapse for the past 5 years were, however, included in the present study); (4) abnormal blood potassium and phosphorus levels; (5) liver, kidney, respiratory, metabolic, or psychological disease; (6) predicted life expectancy of less than 1 year; (7) mental retardation or having parents or legal guardians who were older or had mental disabilities; (8) other disorders that the surgeon considered as inappropriate for participation. The participants were recruited from November 2017 to July 2019.

Randomization and Follow-ups

After evaluating baseline characteristics, the participants were randomized in a 1:1 ratio to the BGS-7 group or the PEEK group. The randomization process was completed by a researcher. Randomization lists were generated using a web program (http://www.randomization.com) and were only accessible to an authorized researcher. Allocation was concealed in opaque envelopes numbered consecutively and presented to the operator immediately prior to surgery. All randomized participants were operated on by a single orthopedic spine surgeon (S.M.P) at our tertiary institution.

Assessments were also conducted at baseline, and the patients were followed up at 3, 6, and 12 months postoperatively to evaluate outcomes. Data on the primary and secondary outcome measures were collected during in-hospital visits or via telephone calls by an independent researcher who was not involved in any other aspect of this trial.

Blinding

This was a single (participant) blind trial that compared between the BGS-7 spacer and PEEK cage in PLIF surgery. Thus, surgeons and assessors for radiographic outcomes were not blinded to the type of surgery. Only the participants and clinical outcome assessor were blinded, and the blinded clinical outcome assessor measured and collected all the clinical outcomes before and after surgery.

Interventions

Posterior lumbar interbody fusion

The bony landmarks of the spine were accurately exposed through a midline longitudinal incision. The pedicle screw was inserted using the conventional freehand technique.[14] After screw insertion, laminectomy and flavectomy were performed to decompress the compressed nerve. Thereafter, discectomy and endplate preparation were performed followed by auto-local bone graft. Two BGS-7 spacers (NovoMax, CGBio Inc., Seongnam, Korea) or PEEK cages (CAPSTONE CONTROL™, Medtronic, Minneapolis, MN, USA) were then inserted according to the assigned group.

Outcomes and measurements

Data on the baseline participant characteristics were collected by researchers blinded to the randomization details. Before randomization, each participant was preoperatively evaluated to obtain demographics, past medical history using the Charlson Comorbidity Index, and the American Society of Anesthesiologists physical status classification. Patient-reported outcomes (PROs) were also collected from participants at baseline and at 3, 6, and 12 months after surgery. The primary outcome measure was the fusion rates on CT at the 12-month follow-up after surgery. Fusion status was defined as the presence of bridging bone and/or the lack of radiolucency at the graft-vertebral junction inside or outside of the cage or spacer on coronal or sagittal planes of the CT image. This evaluation was conducted using a Picture Archiving and Communications System (INFINITT Healthcare Co. Ltd, Phillipsburg, NJ, USA).[15,

16] The coronal and sagittal images were reconstructed using 1.0-mm-interval axial CT scan images of the lumbar spine. Fusion status was evaluated according to the agreement between two orthopedic surgeons (with 7 years and 5 years of experience) who were not involved in the treatment of the patients.

The secondary outcome measures were the clinical, radiographic, and safety outcomes. The clinical outcome measures were the change in the PROs, including visual analog scale (VAS) score for low back and lower extremity radiating pain, Oswestry disability index (ODI), European Quality of Life-5 Dimensions (EQ-5D) score, a nd painDETECT score for neuropathic pain, during follow-up. The radiographic outcome measures were the presence of peri-cage (spacer) osteolysis, cage subsidence, and cage migration. The safety outcome measure was adverse events, such as perioperative complications. VAS questionnaires include a 10-cm line with “none” (0) on one end of the scale and “severe pain” (10) on the other end. The ODI is a specialized questionnaire for lumbar disabilities in a hospital setting. This questionnaire contains 10 questions with 6 responses for each question. Each question is scored on a scale of 0–5, with a score of 5 representing the greatest disability. The ODI score is the total score divided by the total possible score and is expressed as a percentage multiplied by 100. Thus, for all unanswered questions, the total possible score is reduced by 5.[17] The EQ-5D is a general instrument for evaluating health-related quality of life (HRQOL). This questionnaire contains 5 questions with 5 responses for each question, and the total score is converted into the final EQ-5D value, ranging from 0 to 100, with higher scores indicating better HRQOL.[18]

The painDETECT questionnaire is a survey for testing neuropathic pain. It contains 9 questions, with a final score of -1 to 38. A score of less than 12 indicates a likely absence of neuropathic pain, whereas a score of at least 19 indicates a high probability of developing neuropathic pain (> 90%).[19] For the radiographic outcomes, the degree of osteolysis, cage migration and subsidence around the cage (spacer) was evaluated on sagittal or coronal images of reconstruction CT at 12 months after surgery. Other outcome measures were operation time, length of hospital stay, transfusion, intraoperative bleeding, and postoperative drainage. The operation time was the time from skin incision to wound closure. The length of hospital stay was the time from admission to discharge. The postoperative drainage was the total amount of drainage from the Hemovac system (Zimmer Biomet, Warsaw, Indiana, USA). Transfusion was the total packs of blood transfused after the surgery. Intraoperative bleeding was the amount of intraoperative bleeding on the anesthetic record. Adverse events were defined as intraoperative or postoperative complications after surgery and included incidental durotomy, surgical site infection, reoperation, and readmission.

Statistical analysis

For the primary outcome analysis, we calculated that a sample size of 54 participants (27 participants in each group) would provide at least 80% power to show the non-inferiority of bioactive glass-ceramic spacer to PEEK cage, with a one-sided alpha level of 0.05 and a non-inferiority margin of 15% for the 12-month fusion rate of PEEK cage on PLIF surgery, assuming a 20% dropout rate at 12 months.[12, 20] We analyzed the primary and secondary outcome measures based on the per-protocol (PP) strategy, that is, only those who completed the treatment originally allocated were evaluated. For missing observations,

“last value carried forward” was used in this trial. Continuous variables are presented as the mean and standard deviation (SD), whereas categorical variables are presented as numbers and percentages (%). For the primary outcome measure, a one-sided 95% confidence interval (CI) for the group difference was calculated. Non-inferiority of the BGS-7 spacer was confirmed if the lower limit of 95% CI of the fusion rate at 12 months was higher than the pre-defined non-inferiority margin of -15% (fusion rate of PEEK cage group – BGS-7 spacer group ≥ 15%).

For serial measurements of secondary clinical outcomes, a linear repeated-measures mixed model was used. We analyzed time as a categorical variable (3, 6, or 12 months) and included intervention–time interactions to analyze intervention effects at each follow-up point. We also analyzed inter-group differences during the 12- month period, controlling for baseline and follow-up time points as categorical variables, using a linear repeated-measures mixed model. Other secondary outcome measures were compared between the two groups using Student’s t-test for continuous variables or the Fisher’s exact test for categorical variables. Inter-observer and intra-observer agreement were assessed using Cohen’s kappa value (95% confidence interval CI) according to Landis et al.’s method (0.01–0.20, slight agreement; 0.21–0.40, fair agreement; 0.41–0.60, moderate agreement; 0.61–0.80, substantial agreement; and 0.81-1.00, nearly perfect agreement).[21] Two assessors re-analyzed CT scans at 4-week intervals to assess intra-rater agreement. Differences in radiographic results in assigned fusion evaluation for the consensus reading were resolved through joint review of the CT imaging with a unanimous decision.

All statistical analyses were conducted using Stata/MP 15.1 (StataCorp LLC, College Station, TX). A two-sided P-value of < 0.05 was considered statistically significant, except for the P-value from non-inferiority test, which is one-sided.

Results

Participant characteristics

Of the 57 participants assessed for eligibility, 3 participants were excluded. As such, 54 participants who consented to participate were randomized to the PEEK cage group (n = 28 participants) or the BGS-7 spacer group (n = 26 participants). There was no crossover treatment between the groups. After surgery, two participants from each group were excluded because of implant removal surgery due to surgical site infection. Further, 6 and 7 patients in the PEEK cage group and the BGS-7 group, respectively, were lost to follow-up. In total, 15 patients were censored and excluded from the PP analysis. Figure 2 shows the study and follow-up flow chart. The baseline participant characteristics per treatment group are shown in Table 1. There were no significant differences in the baseline clinicoradiographic characteristics between the two groups (all P > .05).

Table 1
Characteristics of the participants at Baseline.

Characteristic	PEEK cage (n = 28)	Novomax (n = 26)
Age (years) *	67.8 (43–80)	63.7 (51–77)
Male / Female†	10 / 18	9 / 17
BMI (kg/m^2)	25.4 ± 3.4	24.7 ± 3.2
CCI score	0.3 ± 0.7	0.3 ± 0.7
ASA score	1.8 ± 0.7	1.8 ± 0.6
Smoking status, n (%)		
Non / Ex-smoker	19 (68%)	17 (65%)
Current smoker	9 (32%)	9 (35%)
Alcohol consumption, n (%)		
None	21 (75%)	18 (69%)
≥ 1 drink/month	7 (25%)	8 (31%)
VAS for back pain	6.8 ± 1.8	5.6 ± 2.8
VAS for leg pain	7.9 ± 1.4	7.0 ± 2.0
ODI	51.3 ± 15.4	48.0 ± 12.5
EQ-5D	0.394 ± 0.141	0.483 ± 0.154
painDETECT	19.5 ± 7.6	17.6 ± 6.1
BMD (T-Score)		
Hip	-1.5 ± 0.9	-1.2 ± 1.0
Lumbar	-0.6 ± 1.7	-0.6 ± 1.4
Diagnosis n (%)		
Central stenosis	19 (68%)	18 (69%)

Data are presented as given as mean ± standard deviation.

*Data are presented as given as mean and range in parenthesis.

†Data are presented as No. of patients.

BMI, body mass index; CCI, Charlson Comorbidity Index; ASA, American Society of Anesthesiologist; VAS, visual analog scale; ODI, Oswestry disability index; EQ-5D, European Quality of Life-5 Dimensions; BMD, bone mineral density

Characteristic	PEEK cage (n = 28)	Novomax (n = 26)
Foraminal stenosis	27 (96%)	24 (92%)
Spondylolisthesis	14 (50%)	15 (58%)
Operation level, n (%)		
L3-4	1 (2.6%)	5 (17.2%)
L4-5	21(53.8%)	17 (58.6%)
L5-S1	17 (43.6%)	6 (20.7%)
Data are presented as given as mean ± standard deviation.		
*Data are presented as given as mean and range in parenthesis.		
†Data are presented as No. of patients.		
BMI, body mass index; CCI, Charlson Comorbidity Index; ASA, American Society of Anesthesiologist; VAS, visual analog scale; ODI, Oswestry disability index; EQ-5D, European Quality of Life-5 Dimensions; BMD, bone mineral density		

Primary outcome

Fusion was achieved in 15 surgical levels in the BGS-7 spacer group (75.0%; 15/20) and in 23 surgical levels in the PEEK cage group (79.3%; 23/29) (Fig. 3). The risk difference between the two groups was − 4.3% (95% CI; -24.5% to + 16.0%). Given that the 95% CI included the 15% non-inferiority margin and zero, the difference is not significant (p = 0.676), and the result regarding non-inferiority of BGS-7 spacer was inconclusive (Fig. 4). The Kappa value for inter-observer reliability was 0.774, which indicated substantial agreement. Meanwhile, the Kappa value for intra-observer reliability was 0.891 and 0.813 in each rater, which indicated nearly perfect agreement.

Secondary outcomes and adverse events

The linear mixed model showed no significant intervention effect in VAS pain score, ODI score, EQ-5D value, and painDETECT score during the 12-month follow-up. There were also no between-group differences in VAS pain score, ODI score, EQ-5D value, and painDETECT score at the 3- and 6-month follow-up (Table 2 and Fig. 5). The operation time, length of hospital stays, transfusion, intraoperative bleeding, and postoperative drainage were also not significantly different (all P > .05).

Table 2
Secondary outcomes and complications for PEEK and BGS-7 groups after surgery during 12-month follow-up

Variables	PEEK	BGS-7	Mean difference (95% CI)	p-value
VAS back				
3 month	3.52 ± 2.65	3.19 ± 2.18	0.33 (-1.11–1.77)	0.649
6 month	3.56 ± 2.39	3.77 ± 2.33	-0.22 (-1.58–1.15)	0.750
12 month	2.83 ± 2.35	3.29 ± 2.52	-0.47 (-2.04–1.10)	0.549
Overall intervention effect*	NA	NA	NA	0.289
VAS lower extremities				
3 month	4.53 ± 3.18	3.24 ± 2.51	1.29 (-0.41–2.99)	0.135
6 month	3.96 ± 2.95	3.29 ± 2.78	6.77 (-1.01–2.36)	0.423
12 month	3.43 ± 3.22	3.35 ± 2.45	0.08 (-1.81–1.97)	0.931
Overall intervention effect*	NA	NA	NA	0.681
ODI				
3 month	29.87 ± 18.45	24.62 ± 18.65	5.25 (-6.05–16.55)	0.354

VAS, visual analog scale; NA, not available; ODI, Oswestry disability index; EQ-5D, European Quality of Life-5 Dimensions

Data are presented as given as mean ± standard deviation, unless otherwise indicated.

*P-value is from linear mixed models for repeated measures comparing between interventions during 12-month follow-up period.

†The Fisher's exact test was used and the values are presented as numbers and percentages (%).

Variables	PEEK	BGS-7	Mean difference (95% CI)	p-value
6 month	26.46 ± 12.52	26.65 ± 16.77	-0.19 (-9.11–8.73)	0.966
12 month	21.27 ± 15.93	26.82 ± 17.64	-5.55 (-16.47–5.37)	0.310
Overall intervention effect*	NA	NA	NA	0.270
EQ-5D				
3 month	0.697 ± 0.191	0.765 ± 0.169	-0.676 (-0.173–0.039)	0.207
6 month	0.732 ± 0.154	0.714 ± 0.173	0.017 (-0.077–0.111)	0.713
12 month	0.767 ± 0.160	0.738 ± 0.116	0.029 (-0.064–0.121)	0.535
Overall intervention effect*	NA	NA	NA	0.095
painDETECT				
3 month	10.23 ± 8.48	5.90 ± 4.47	4.33 (0.20–8.46)	0.041
6 month	7.54 ± 8.02	6.23 ± 5.80	1.31 (-2.82–5.45)	0.526
12 month	6.00 ± 6.16	7.94 ± 6.12	-1.94 (-5.92–2.04)	0.330
Overall intervention effect*	NA	NA	NA	0.152
Adverse events, No. (%)†				

VAS, visual analog scale; NA, not available; ODI, Oswestry disability index; EQ-5D, European Quality of Life-5 Dimensions

Data are presented as given as mean ± standard deviation, unless otherwise indicated.

*P-value is from linear mixed models for repeated measures comparing between interventions during 12-month follow-up period.

†The Fisher's exact test was used and the values are presented as numbers and percentages (%).

Variables	PEEK	BGS-7	Mean difference (95% CI)	p-value
Severe adverse events	0	1 (3.8%)		1.000
Incidental durotomy	5 (17.9%)	4 (15.4%)		1.000
Surgical site infection	1 (3.6%)	1 (3.8%)		1.000
Revision surgery due to pedicle fracture	1 (3.6%)	0 (0%)		1.000
VAS, visual analog scale; NA, not available; ODI, Oswestry disability index; EQ-5D, European Quality of Life-5 Dimensions				
Data are presented as given as mean ± standard deviation, unless otherwise indicated.				
*P-value is from linear mixed models for repeated measures comparing between interventions during 12-month follow-up period.				
†The Fisher's exact test was used and the values are presented as numbers and percentages (%).				

For radiographic outcomes, osteolysis was 6 surgical levels (21.4%) in the PEEK cage group and 7 surgical levels (25%) in the BGS-7 spacer group, with no significant intergroup difference (p = 0.496). Spacer migration was found in 2 cases in the BGS-7 spacer group. One spacer migrated backward to the posterior canal, and the other migrated forward to the anterior vertebral body. One spacer has a fracture in the middle of the spacer. Meanwhile, the upper and lower endplate subsidence were 2.46 mm (± 1.69) and 2.60 mm (± 1.53) in the PEEK cage group and were 0.77 mm (± 1.10) and 0.76 mm (± 1.16) in the BGS-7 spacer group, respectively, with significantly lower values in the BGS-7 spacer group (p < .05) (Table 3).

Table 3
Radiographic parameters for for PEEK and BGS-7 groups at 12-month follow-up

Variables	PEEK	BGS-7	p-value
Osteolysis, No (%) *	6 (21.4%)	7 (25.0%)	0.496
Spacer migration, No (%)*	0 (0%)	2 (7.7%)	0.491
Spacer fracture, No (%)	0 (0%)	1 (3.8%)	1.000
Subsidence†			
Upper endplate	2.46 ± 1.69	0.77 ± 1.10	0.001
Lower endplate	2.60 ± 1.53	0.76 ± 1.16	0.000
Data are presented as given as mean ± standard deviation, unless otherwise indicated.			
*The Fisher's exact test was used and the values are presented as numbers and percentages (%).			
†p-value is from independent t-test comparing between interventions during 12-month follow-up period.			

In total, 7 (25%) and 6 (23.1%) participants in the PEEK cage and BGS-7 groups, respectively, experienced more than one adverse reaction, with no significant differences between the two groups. One participant in the BGS-7 spacer group had a postoperative stroke but recovered, and this event was not related to the medical device. Incidental durotomy occurred in 4 patients in the BGS-7 spacer group and in 5 patients in the PEEK cage group, but no clinical problem occurred. One surgical site infection occurred in each group, and reoperations were performed to remove the medical device. In the PEEK cage group, one pedicle fracture occurred after surgery and reoperation was performed (Table 2).

Discussion

PEEK and titanium are the most widely used cage materials in PLIF, with satisfactory results and a high fusion rate.[22] However, PEEK cages are also associated with complications. Thus, this trial investigated the non-inferiority of BGS-7 spacers to PEEK cages. The non-inferiority of BGS-7 spacer compared to PEEK cage was inconclusive. However, the fusion rates, clinicoradiographic outcomes, and adverse events of the BGS7 spacer were similar to those of the PEEK cage.

The intervertebral cage in PLIF surgery is intended to maintain intervertebral disc space stability and facilitate intervertebral fusion.[1–3] An ideal interbody spacer for PLIF is one with a similar elastic modulus to the bone while providing stability and achieving a high fusion rate. PEEK cages have several advantages over other synthetic cages. First, because it is radiolucent, it is easy to perform x-ray and CT scans when evaluating the fusion status after surgery, and magnetic resonance imaging can also be easily performed because there are limited implant artifacts. Second, the PEEK cage has a similar elastic modulus to that of the bone, and thus, the cage subsidence is lower and the load is evenly distributed

between the bone and the cage.[23, 24] However, the PEEK cage does not have bone conduction and bone induction properties and therefore cannot directly fuse with the bone. To overcome these limitations, autobone and bone substitute materials such as allobone, demineralized bone matrix, and hydroxyapatite (HA), are used inside the PEEK cage. However, although materials incorporating various bone substitute materials inside the PEEK cage are used, data on these materials are still limited.[4, 24]

Compressive strength is an important characteristic of intervertebral disc spacers because it is related to the resistance to intraoperative damage and repetitive loads after surgery. HA spacers have been reported to have a weak compressive strength and are thus greatly damaged during surgery. BGS-7 spacers have stronger mechanical strength than do HA spacers and are also slightly stronger than PEEK and titanium cages.[11] In this study, only one case of BGS-7 spacer fracture occurred, which was not statistically significant. Subsidence occurs when the mechanical strength is high, but the results of this study show lesser subsidence in BGS-7 spacers than that in PEEK cages. This result is thought to be due to the specific characteristics of the PEEK cage (CAPSTONE CONTROL™, Medtronic) used in this study (rotation in the intervertebral space) rather than the general characteristics of the PEEK cage. The degree of subsidence in this study is excellent at less than 1 mm and is similar to that in previous studies.[12] Further, the mechanical properties is judged to only have a slight effect on subsidence. Two BGS-7 spacer migrations occurred in our study, but this was not caused by the mechanical properties of the spacer and is rather considered to be a spacer design problem. Specifically, it is caused by the smooth upper and lower surfaces of the spacer (Fig. 1), and this design problem needs to be corrected.

Spacers made of bone graft substitutes such as bioactive glass ceramics are currently being studied as alternatives to cages in which bone substitutes are fused. The BGS-7 spacer has a high bioactive capacity, showing chemical bonding capability.[6, 25] In a previous clinical study, the 12- and 48-month union rates on CT were 89.7% and 90.6%, respectively, in the BGS-7 spacer group and were similar to those in the titanium group.[12, 26] The 12-month fusion rate of the BGS-7 spacer group in this study is slightly lower than that in the previous study at 75.0%. There was no significant difference in the fusion rate compared to that of the PEEK cage, but the 95% CI range included the noninferiority limit and zero, and thus, the result was inconclusive. However, not only the fusion rate, but also the radiographic outcomes, clinical outcomes, and adverse events were similar to those of the PEEK cage. Collectively, these results support that BGS-7 spacers can be an alternative to PEEK cages. Given that the BGS-7 spacer has a wide contact surface and can bond directly to the bone, the fusion area of the end plates is much wider in the BGS-7 spacer than that in the PEEK cage. The large fusion area plays an important role in the stress distribution of the spacer in interbody fusion and has biomechanical advantages because it effectively distributes the load on the vertebral body to lower the subsidence rate.[27, 28] In this study, the bone fusion rate of the BGS-7 spacer was not higher than that of the PEEK cage, but in theory it is considered to be more advantageous than the PEEK cage.

The CaO-SiO2-P2O5-B2O3 glass ceramic is a new material made for spacer. A toxicity study in previous animal experiments showed no specific side effects even in high-dose intravenous injections of an aqueous extract of CaO-SiO2-P2O5-B2O3 glass ceramic for 90 days.[10] The rapid absorption of glass

ceramics in the body has a negative effect on its role as a bone conduction support, but CaO-SiO2-P2O5-B2O3 glass ceramics have very low bio-absorption.[29] In addition, CaO-SiO2-P2O5-B2O3 glass ceramics are highly unlikely to cause adverse tissue reactions or systemic reactions even if it remains in the body after surgery. Thus, they are safe to use as spacers. No device-related severe adverse events were found in this study during the 1-year follow-up period, but a longer follow-up is necessary because the substance is present in the body for a long time.

To our best knowledge, this is the first trial to compare the clinicoradiographic outcomes between BGS-7 spacers and PEEK cages at 12 months after surgery. However, our trial has some limitations. First, this trial had a small sample size, which prevents more generalized conclusions on the potential differences between the two interventions. The initial sample size calculation determined 27 participants would be necessary in each group, with a 20% drop out rate. The findings may be inconclusive because of the small number of participants included in the follow-up. However, the final fusion rate and other outcomes were measured similarly. We cannot conclude that the outcomes of BGS-7 spacers and PEEK cages were similar, but they may be replaceable. Second, the 12-month end-point of our trial was inadequate to assess the advantages and disadvantages of BGS-7 spacers for PLIF surgery. Thus, we are planning to continue the follow-up. Third, this study is a single-blind study in which only the participants were blinded to the intervention. Although the assessor who collected the data on clinical outcomes was also blinded to the group allocation, it was impossible to maintain blinding of the assessor who evaluated the radiographic outcomes. To lower the impact of this limitation, the fusion rate was evaluated by a third-party investigator not involved in the study. Thus, it is unlikely that the assessor judgment will has affected the results of this study. Finally, multiple comparisons were used in the analysis of clinical outcomes. Caution should be taken when interpreting the statistical effects of interventions as these multiple comparisons increase the risk of type 1 errors.

Conclusion

In this randomized controlled trial of participants who underwent PLIF surgery, BGS-7 spacers had similar fusion rates, clinical and radiographic outcomes, and adverse events to those of PEEK cages at 12 months after surgery. However, results on the non-inferiority of BGS-7 spacers to PEEK cages were inconclusive. The findings indicate that BGS-7 spacers can be a feasible and safe alternative to PEEK cage in PLIF surgery after further studies.

Abbreviations

BGS-7: The CaO-SiO2-P2O5-B2O3 glass-ceramic

PEEK: polyetheretherketone

PLIF: posterior lumbar interbody fusion

VAS: Visual analog scale

ODI: Oswestry Disability Index

EQ-5D: European Quality of Life-5 Dimensions

HRQOL: health-related quality of life

CT: computer tomography

PROs: Patient-reported outcomes

PP: per-protocol

SD: standard deviation

CI: confidence interval

Declarations

Ethics approval and consent to participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of the Seoul National University Bundang Hospital Institutional Review Board of Human Study Committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consents were obtained from all patients.

Consent for publication

Not applicable.

Availability of data and material

All data concerning the case are presented in the manuscript.

Competing interests

The authors declare no competing interests.

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Authors' contributions

BT K and HJ K equally contributed to drafted and revised the manuscript. SM P designed the study and was the surgeon who performed all of operations. All authors read and approved the final manuscript.

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Figures

Figure 1

Photographs of implants: CaO-SiO2-P2O5-B2O3 bioactive glass ceramic spacer for lumbar interbody fusion

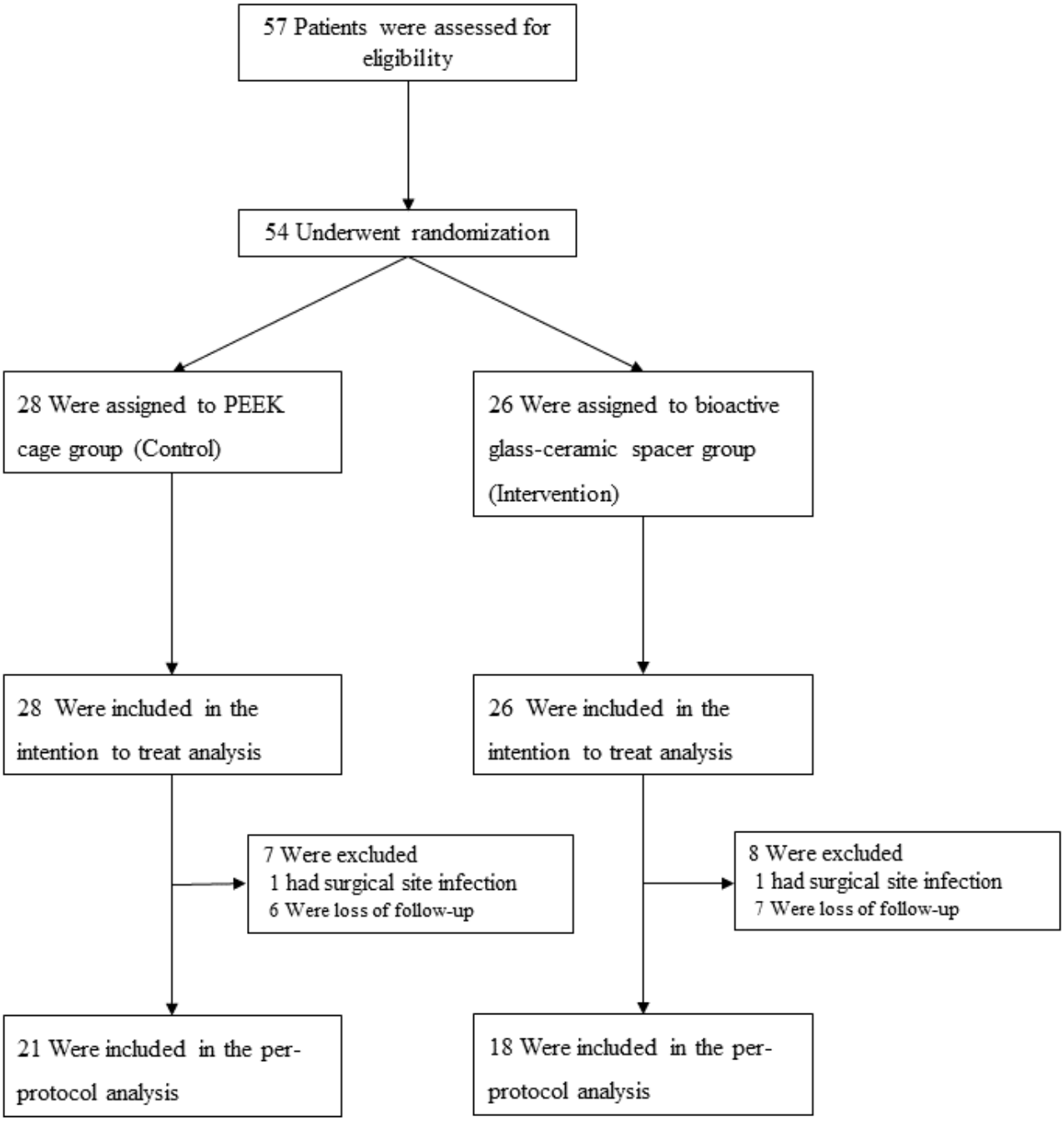

Figure 2

Flow chart for enrollment, randomization, treatment, and follow-up.

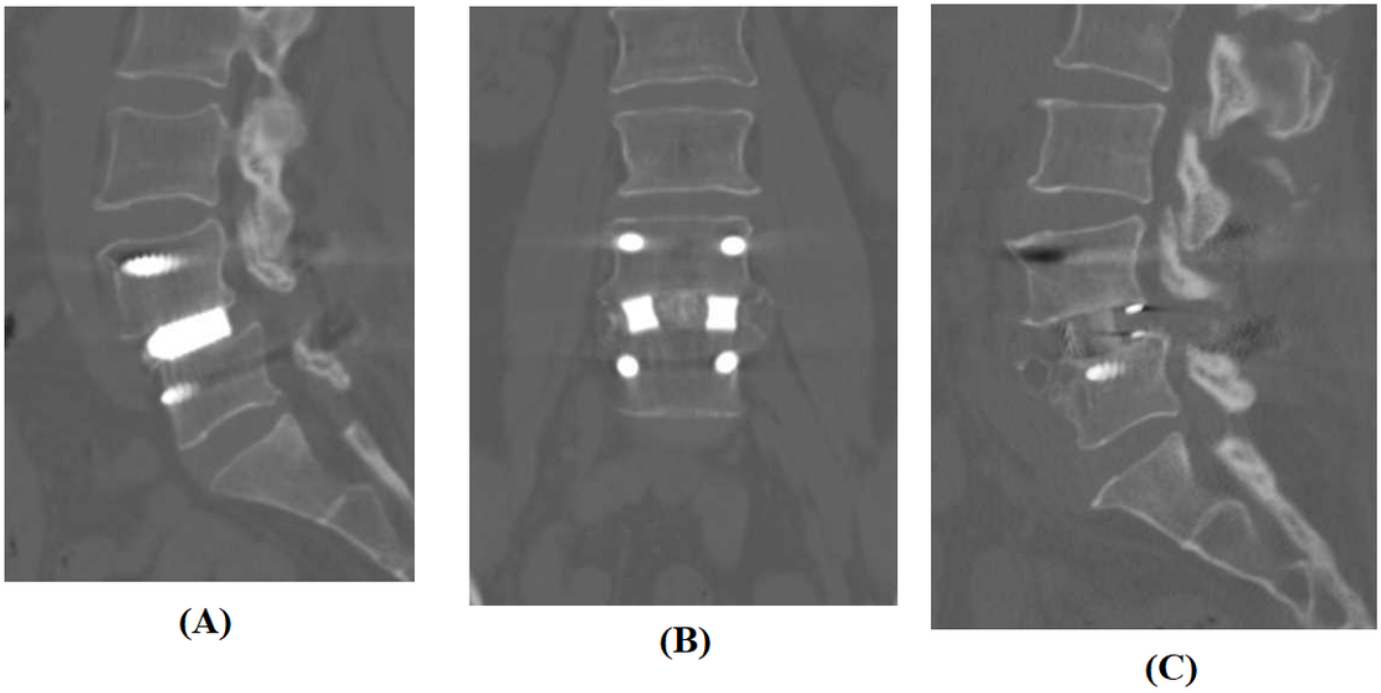

Figure 3

Sagittal and coronal computed tomography scans taken 12 months postoperatively shows complete fusion of BGS-7 spacer (A, B) and PEEK cage (C, D).

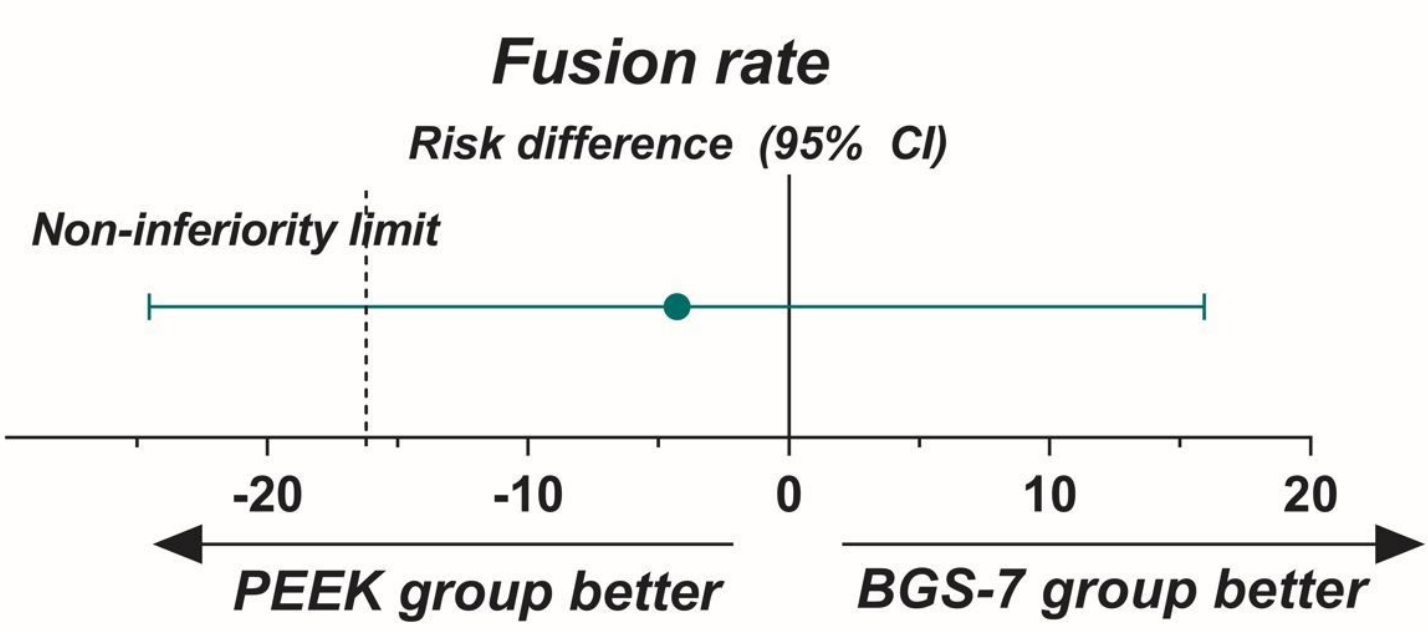

Figure 4

Graph showing the lack of difference in fusion rate between the two groups at 12 months after surgery (p=0.676). The dash-line indicates the non-inferiority margin of −15%. Given that the 95% CI of the difference included the 15% non-inferiority margin and zero, the result regarding non-inferiority of BGS-7 spacer is inconclusive.

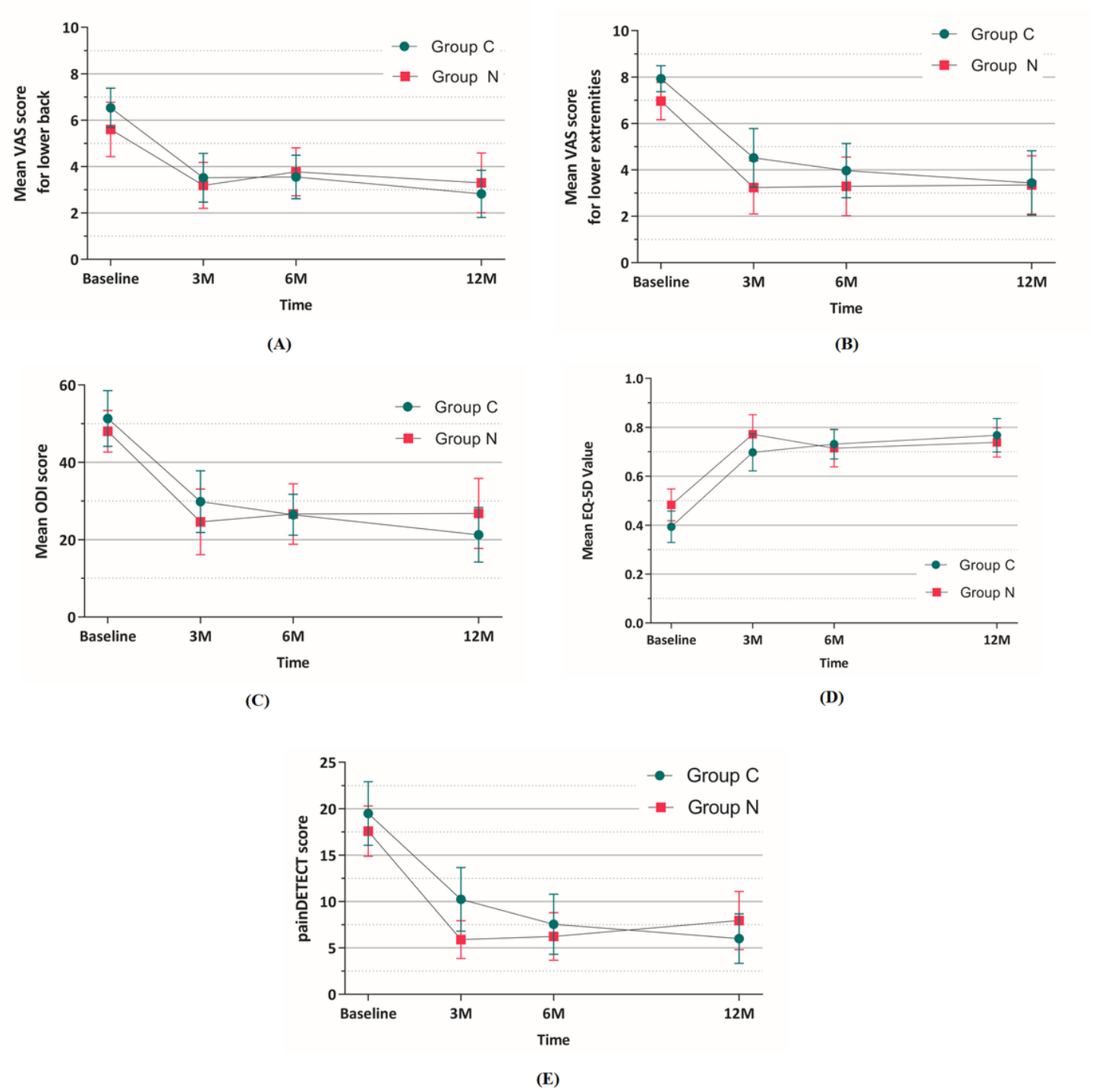

Figure 5

Changes in secondary outcomes in the two groups during the 12-month follow-up period. (A) Changes in mean VAS low back pain score, ranging from 0 (no pain) to 10 (worst pain). (B) Changes in mean VAS lower extremities pain score, ranging from 0 (no pain) to 10 (worst pain). (C) Changes in mean ODI score, ranging from 0 (no disability) to 100 (high disability). (D) Changes in mean EQ-5D value, ranging from 0 (worst quality of life) to 100 (best quality of life). (E) Changes in mean painDETECT, with higher scores

indicating severe neuropathic pain. Error bars indicate 95% confidence intervals. VAS, visual analog scale; ODI, Oswestry disability index; EQ-5D, European Quality of Life-5 Dimensions