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Usefulness of Synthetic Osteoconductive Bone Graft Substitute with Zeta Potential Control for Intramedullary Fixation with Proximal Femur Nail Antirotation in Osteoporotic Unstable Femoral Intertrochanteric Fracture

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Purpose: This study was conducted in order to examine the usefulness of osteoconductive bone substitutes with zeta potential control (geneX® ds; Biocomposites, England) by comparing the complications and radiographic evaluation with or without geneX® ds augmentation for internal fixation with proximal femur nail antirotation (PFNA) for treatment of osteoporotic unstable intertrochanteric fractures.

Materials and Methods: A retrospective study of 101 patients who underwent fixation with PFNA in osteoporotic unstable intertrochanteric fractures was conducted from December 2015 to August 2020. The radiographic evaluation and complication rates were compared between patients with geneX® ds (Group A: 41 cases) and those without geneX® ds (Group B: 60 cases).

Results: In radiological valuation, the degree of blade sliding from the time immediately after surgery to one year after surgery was 1.4±1.2 mm and 5.8±2.7 mm in Group A and Group B, respectively (P<0.001). During the same time frame, a significant difference of 2.3±2.2˚ and 7.4±3.1˚, respectively (P<0.001), in varus collapse, was observed for Group A and Group B.

Conclusion: Among patients fixed with PFNA for treatment of unstable intertrochanteric fractures, less blade sliding and varus collapse was observed for those with geneX® ds augmentation compared to those without it. In addition, there was no increase in the incidence of complications. The authors believe it can be regarded as a safe and effective additive for intramedullary fixation for treatment of unstable intertrochanteric fractures.

Key Words: Hip fracture, Intramedullary fixation, Bone substitutes

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INTRODUCTION

A femoral intertrochanteric fracture is an extra-capsular hip fracture, mainly occuring in elderly patients with osteoporosis. The prevalence of femoral intertrochanteric fractures has shown a recent increase due to the increase in adults with osteoporosis[1,2]. In elderly patients, the goal in treatment of intertrochanteric fracture is recovery of the patient's activity to the level before the fracture as soon as possible. This can be achieved through prevention of complications related to fractures through anatomical reduction and rigid internal fixation and by obtaining early union[3].

Good results can be obtained in stable fractures by internal fixation with dynamic hip screws (DHS)[4]. However, the complications that might occur in unstable fractures are as follows: postoperative varus collapse, nonunion, and periprosthetic fractures[5]. Use of calcium phosphate[6] or polymethylmethacrylate (PMMA)[7] as augmentation with the fixation of intertrochanteric fractures has been described in previous studies. β-Tricalcium phosphate (β-TCP), which is a more bio-friendly material compared to bone cement, is helpful in cell differentiation, bone formation, and bone conduction[8]. However, research related to β-TCP augmentation in unstable femoral intertrochanteric fractures is insufficient.

The aim of this study was to examine the usefulness of zeta potential control (geneX® ds; Biocomposites, Staffordshire, England) by comparing the radiographic results and complications between groups with and without geneX® ds augmentation during an intramedullary fixation with proximal femur nail antirotation (PFNA; Synthes, Paoli, Switzerland) for treatment of osteoporotic unstable intertrochanteric fractures.

MATERIALS AND METHODS

1. Patient Selection

This is a retrospective case-control study. The study protocol was approved by the Ethics Committee of the Research Institute of Busan Bumin Hospital (202108-BM-001), and the informed consent was waived by the Ethics Committee. Close reduction and internal fixation of the unilateral intertrochanteric fracture were performed in 168 cases from December 2015 to August 2020. The exclusion criteria were as follows: 1) age younger than 60 years old (n=12), 2) high-energy trauma (n=3), 3) osteoporosis (T-score of –2.5 or less in bone mineral density [BMD]) (n=10), 4) stable intertrochanteric fracture (n=2), and 5) follow-up loss including deceased cases within one year (n=40). After exclusion of cases, 101 cases were finally enrolled in this study.

The definition of the stability of the fracture was based on the Evans classification[9]. The geneX® ds-use and non-use groups were labeled as Group A and Group B, respectively. Group A included 41 patients (41 cases) and Group B included 60 patients (60 cases). The mean follow-up period was 14.6 months (range, 12-36 months).

The mean follow-up period was 13.9 months (range, 12-36 months) and 14.8 months (range, 12-32 months) in Group A and Group B, respectively. A summary of the patient demographics is shown in Table 1.

2. Surgical Technique and Rehabilitation

All surgeries were performed by two experienced orthopedic surgeons. All patients underwent closed reduction by traction in the supine position on the fracture table. The status of the reduction and the position of fixative devices were checked under fluoroscopic guidance using a C-arm. The tip-apex distance (TAD) was measured to evaluate the location of the lag screw. The operator attempted to locate the tip of the guidewire within 5 mm of the subchondral bone. The needle was inserted along the reamed track made for the blade in the femoral head and neck and the cancellous bone defect around the fracture. A total of 5 mL of Genex® ds was injected through the needle, which was confirmed using the C-arm (Fig. 1).

Patients were allowed to be in a sitting position from postoperative day (POD) 1, and passive joint movement was allowed after removal of the draining tube from POD 2 to 3. Quadriceps femoris strengthening, as well as leg raising exercises, were performed as soon as possible. Patients were then allowed to go to the bathroom carefully in a wheelchair. Full weight-bearing ambulation without assistance was allowed at least six weeks after surgery.

3. Clinical Evaluation

Clinical evaluation using the Harris hip score (HHS) was performed at three months, six months, and one year after surgery.

4. Radiologic Evaluation

The radiographic evaluation was performed by two expe-

Table 1. Patient Demographics

Characteristic	Group A (n=41)	Group B (n=60)	*P*-value
Age (yr)	75.1±7.2	77.7±6.9	0.13
Sex			0.11
Female	26	41	
Male	15	19	
Side			0.69
Left	18	22	
Right	23	38	
Bone mineral density (T-score)	−2.9±0.3	−3.1±0.9	0.11
Fogagnolo classification			0.48
Good	21	37	
Acceptable	20	23	
Poor	0	0	
Follow-up duration (mo)	13.9±3.7	14.8±2.9	0.61

Values are presented as mean±standard deviation or number only.
Statistical significances ($P<0.05$) were tested by independent *t*-test for analysis of continuous variables (age, body mass index), and the chi-square test for the analysis of independent variables (sex, side) between groups.
Group A: geneX® ds augmentation, Group B: non geneX® ds.

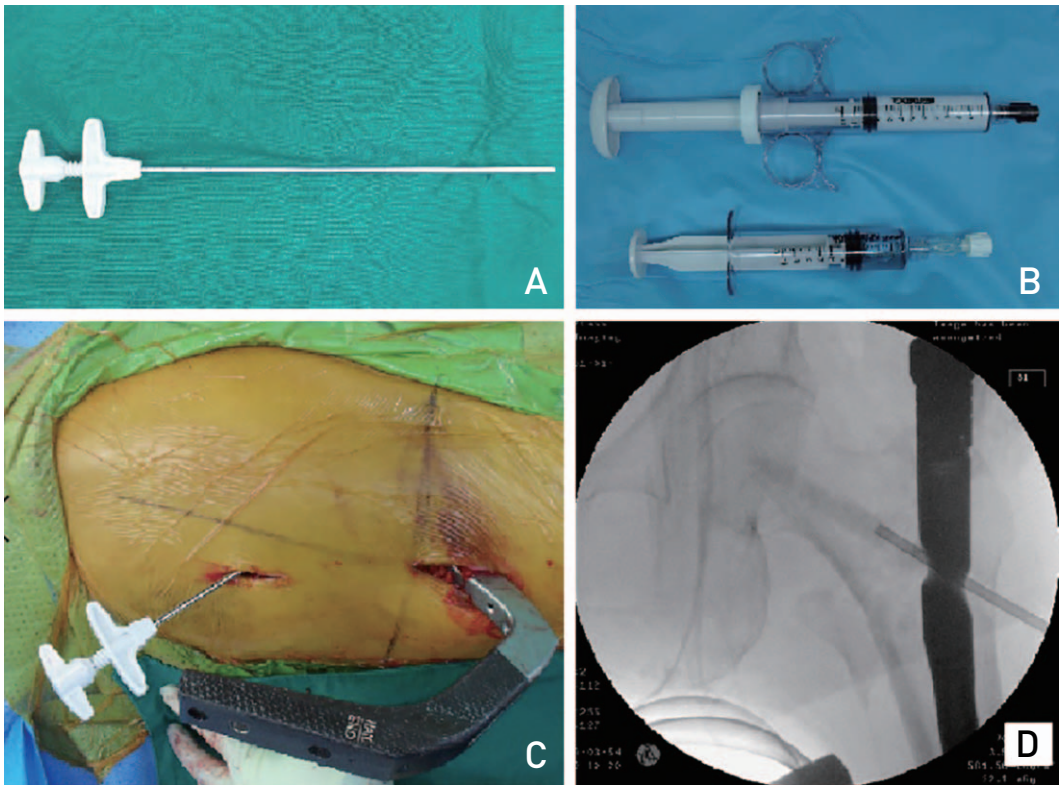

Fig. 1. geneX® ds (5 cc) injected into the femoral head where the helical blade will be inserted in fracture site through the guide wire. (**A**) Guide wire. (**B**) Powder and the liquid of geneX® ds. (**C**, **D**) geneX® ds (5 cc) inserted below the guide pin to the reamed track made for the blade inside the femoral head and neck and severe cancellous bone defect area around the intertrochanteric fracture.

rienced orthopedic surgeons using the picture archiving and communication system (PACS). Dual-energy X-ray absorptiometry was used for assessment of BMD. The mean bone density in the first to fourth lumbar spine was used. If vertebroplasty was performed, the mean value excluding the site of operation was used. In the proximal femur, bone

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density of the femoral neck or total femur was collected. The lowest value among the three was defined as the patient's BMD.

The radiologic evaluation was performed twice, and the mean was used as a representative value. The Cleveland index was used to evaluate the position of the implant[10]. Location of the lag screw in areas 5-8 was defined as acceptable, otherwise it was defined as poor. The TAD was measured to evaluate the position of the lag screw. Fogagnolo's classification was used to assess the accuracy of reduction[11]. To reduce measuring error, the anteroposterior (AP) radiograph was taken with the patients' lower extremity set in 15˚ of internal rotation. The authors used the width of the lesser trochanter to standardize the rotation of the proximal femur.

AP and lateral plain radiographs were obtained immediately after surgery and at six weeks, three months, six months, and one year after surgery. The mean blade sliding length and the degree of varus collapse were measured. Fixation failure, time of bone union, and periprosthetic fracture or osteonecrosis around the implant were assessed.

The intraclass correlation coefficient (ICC) was used to determine the inter-observer reliability. Excellent inter-observer reliability was observed for two tests, sliding of screw (ICC=0.91) and varus collapse (ICC=0.85). Good inter-observer reliability was observed for Union time (ICC=0.71) and TAD (ICC=0.78).

Blade sliding was defined as the distance between the edge of the blade and the neck shaft junction on plain AP radiographs[12]. The distance was measured immediately after surgery andone year after surgery. Varus collapse was measured by the decline of the neck-shaft angle on plain AP radiographs immediately after surgery and one year after surgery (Fig. 2). The criteria for bone union were defined as at least three cortical bones showing callus bridging in the AP and lateral plain radiographs.

5. Complication Evaluation

The patients' medical records were reviewed to evaluate complications. Postoperative deep or superficial infection, delirium, urinary tract infection, cardiovascular problems including venous thromboembolism, pneumonia, intestinal obstruction, and blood transfusion were recorded.

6. Statistical Analysis

Statistical analysis was performed using bundled software (IBM SPSS ver. 20.0; IBM, Armonk, NY, USA). Fisher's exact test was used for analysis of categorical variables, and the Student's *t*-test was used for evaluation of numerical variables. Statistical significance was set at $P<0.05$.

RESULTS

A summary of the change in HHS after the operation is shown in Table 2. No difference in TAD, the Cleveland index, and the time for union was observed between the groups. However, there was a statistically significant difference in sliding a blade and change in the neck-shaft angle (Table 3). There was no periprosthetic fracture or osteonecrosis in either group (Table 3). Uneventful healing of the fracture was observed in most cases (Fig. 3). In Group B, there was one case of fixation failure caused by a cut through to the femoral head. In this case, conversion to a

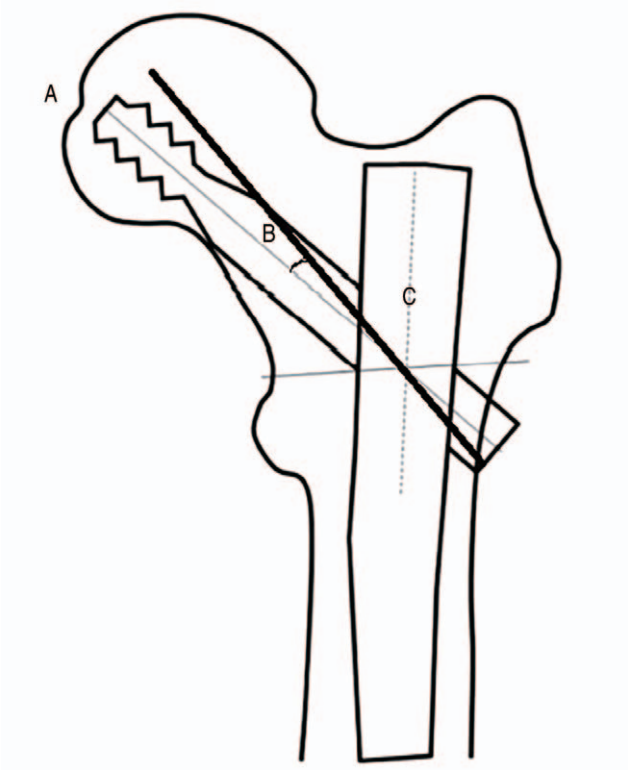

Fig. 2. Radiographic measurement of blade sliding and varus collapse. Measurement of the sliding length. The sliding length was calculated by subtracting length of 'AC' between immediated postoperative radiograph and postoperative 1 year radiograph. Measurement of the varus collapse. 'B': angle between neck axis and screw axis. The varus collapse change was calculated by substracting angle 'B' between immediate postoperative radiograph and postoperative 1 year radiograph.

total hip arthroplasty was performed at six weeks after the indexoperation (Fig. 4). A summary of postoperative complications is shown in Table 4, and there were no significant differences in the occurrence of any complications (Table 4).

DISCUSSION

The usefulness of Genex® ds, which is the synthesis of β-TCP and calcium phosphate, was demonstrated in this study.

β-TCP is an aseptic artificial material and a bone sub-

Table 2. Functional Outcomes for Group A and Group B

Harris hip score	Group A (n=41)	Group B (n=60)	*P*-value
Postoperative 3 months	46.1±7.67	42.1±6.12	0.17
Postoperative 6 months	63.4±5.88	59.2±6.52	0.09
Postoperative 1 year	75.1±5.63	70.1±5.01	0.12

Values are presented as mean±standard deviation.
Statistical significances ($P<0.05$) were tested by independent *t*-test for analysis of continuous variables.
Group A: geneX® ds augmentation, Group B: non geneX® ds.

Table 3. Radiographic Outcomes for Group A and Group B

	Group A (n=41)	Group B (n=60)	*P*-value
TAD (tip-apex distance) (mm)	16.5±4.2	16.1±3.8	0.22
Cleveland index (acceptable/poor)	34/7	51/9	0.31
Sliding of screw (mm)	1.4±1.2	5.8±2.7	<0.001*
Varus collapse (°)	2.3±2.2	7.4±3.1	<0.001*
Union time (wk)	18.1±2.4	22.8±3.0	0.12
Periprosthetic fracture (n)	0	0	
Avascular head necrosis (n)	0	0	

Values are presented as mean±standard deviation or number only.
Statistical significances (*$P<0.05$) were tested by independent *t*-test for analysis of continuous variables (sliding of screw, varus collapse, union time).
Group A: geneX® ds augmentation, Group B: non geneX® ds.

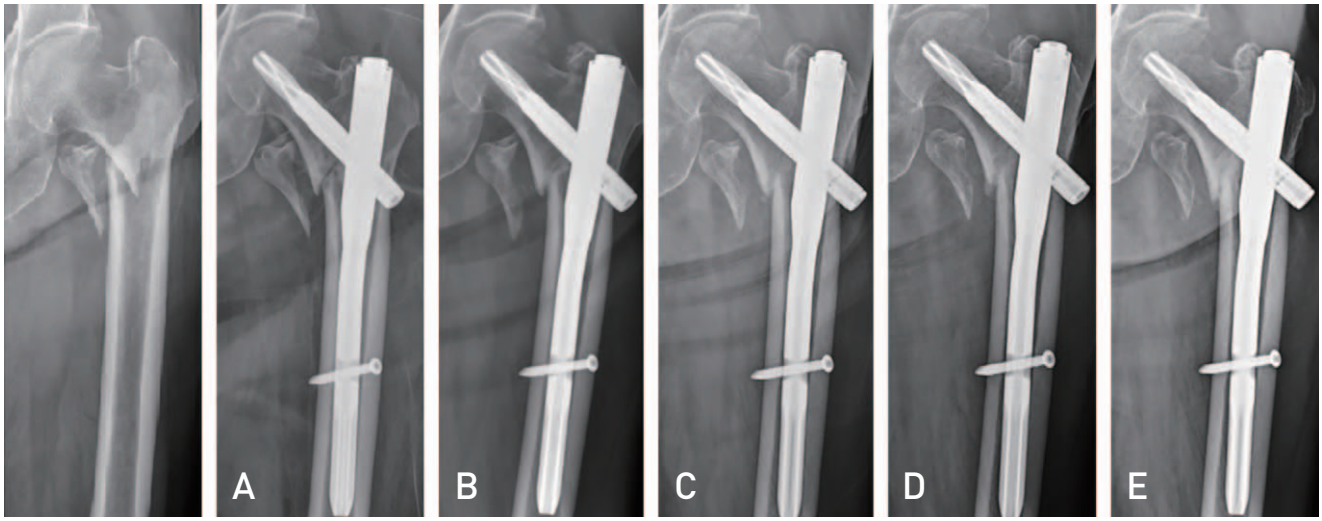

Fig. 3. Serial follow-up X-ray of the 82-year-old female patient. Preoperative radiograph shows trochanteric fracture. (**A**) Immediate postoperative radiograph after surgery with geneX® ds augmentation. (**B**) Postoperative radiograph at the 6-week follow-up. (**C**) Postoperative radiograph at the 3-month follow-up. (**D**) Postoperative radiograph at the 6-month follow-up. (**E**) Postoperative radiograph at 1-year follow-up. Blade sliding: 6.9 mm, varus collapse: 2.9°.

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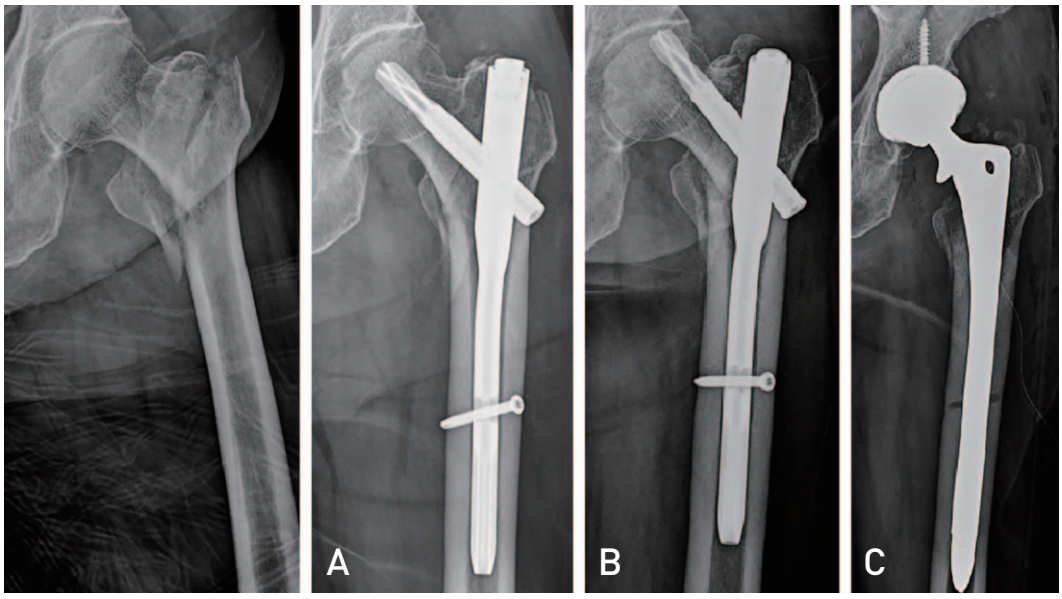

Fig. 4. Serial follow-up X-ray of the 77-year-old female patient. Preoperative radiograph shows trochanteric fracture. (**A**) Immediate postoperative radiograph after surgery without geneX® ds augmentation. (**B**) Postoperative radiograph at the 6-week follow-up (proximal femur nail antirotation [PFNA] cut out state). (**C**) Immediate postoperative radiograph after conversion total hip arthroplasty.

Table 4. Postoperative Complications

Complication	Group A (n=41)	Group B (n=60)	*P*-value
Superficial infection	2	2	0.51
Deep infection	0	0	
Wound dehiscence	2	1	0.38
Delirium	10	25	0.33
Urinary tract infection	4	9	0.22
Thrombosis	1	0	>0.99
Cardiovascular event	0	1	0.79
Pneumonia	1	4	0.63
Ileus	0	4	0.77
Transfusion	11	30	0.45

Values are presented as number only.
Statistical significances ($P<0.05$) were tested by Fisher's exact test between groups.
Group A: geneX® ds augmentation, Group B: non geneX® ds.

stitute that can reduce the risk of infection by blood or tissue transplantation. β-TCP has recently been used as an artificial bone substitute for bone grafts due to its faster absorption compared with calcium phosphate, promoting osteogenesis and being replaced by autogenous bone after the elution and absorption process[13].

geneX® ds is a recently developed synthetic osteoconductive bone substitution with a 1:1 ratio of calcium sulfate and β-TCP, which has a unique characteristic called zeta potential control (ZPC®) that provides the surface with a negative charge. Therefore, proteins and bone-forming cells are pulled to the surface of geneX® ds[14]. One study reported that there was no significant difference in union time with geneX® ds augmentation after high tibial osteotomy compared with autologous bone grafts[15]. Another study reported that geneX® ds augmentation reduces blade sliding distance in patients with unstable femoral intertrochanteric fractures and promotes bone union[16]. However, research related to the use of geneX® ds in treatment of unstable femoral intertrochanteric fractures is insufficient.

This study compared the radiologic evaluations and complications between patients with and without geneX® ds

augmentation in 101 patients with osteoporotic unstable femoral intertrochanteric fractures.

Shin et al.[16] reported that the use of geneX® ds had a positive effect on blade sliding. Similarly, the blade sliding distance was decreased one year postoperatively with geneX® ds augmentation. This indicates that if a satisfactory reduction is achieved after an unstable intertrochanteric fracture, geneX® ds augmentation can have a positive effect on bone healing.

This is thought to be due to the fact that before fracture healing, the implant sustains most of the mechanical loads, however geneX® ds augmentation can cause a load dispersion effect.

We also observed a significant decrease in varus collapse with geneX® ds augmentation. This was considered when geneX® ds augmentation stabilized the fracture site. This is thought to be due to the strong mechanical properties of calcium sulfate against the compressive force. In addition, a mechanical property is promoted due to the high osteoinductive and osteoconductive properties of β-TCP. Therefore, it has a positive effect on varus collapse that may occur during weight-bearing.

These results regarding blade sliding and varus collapse are believed to be due to the additional mechanical property of geneX® ds augmentation in osteoporotic bone.

Thera are several risk factors of metal failure. First, intraoperative surgeon-related factors: damage to the femoral head by over-reaming, malposition of the lag screw. Second, intraoperative fracture-related factors: lateral buttress deficiency, unstable medial cortex, and mal-reduction in varus position. Third, technical mistakes: too great TAD, superior/anterior placement of the lag screw in the femoral head, and inadequate lag screw length.

Previous studies have demonstrated that the use of bone cement in femoral intertrochanteric fracture does not reduce bone union time[16]. However, although not statistically significant, the bone union time tended to decrease in our study. It is thought that β-TCP was absorbed into the body before the bone union occurred, and thus had little effect on the biologic effect. This is probably because it mainly entered the tract where the blade enters rather than the area of the bone defect. This is believed to be due to the small number of samples, which should be confirmed through conduct of a large-scale study.

Friesenbichler et al.[17] reported five complications (16%) in 31 patients, including delayed wound healing, aseptic inflammation of the tendon, and local pain around geneX® ds. However, no significant differences in complications such as infection, wound dehiscence, and local pain related to geneX® ds were identified in our study.

There are several limitation in our study. First, limitations of this study include the small number of cases. It was confirmed that bone union time may be shortened by geneX® ds augmentation, however its statistical significance was not proven, and that the follow-up period was relatively short due to the elderly patients. Third, in selection of patients, it would be better to include all patients over 65 years, the criteria for the elderly, to further enhance the credibility of the study results.

However, geneX® ds has potential use as a biofriendly material compared with bone cement, and it is believed that large-scale research will be needed in the future as it can be theoretically expected that superior clinical results will be obtained. geneX® ds augmentation will be a sufficiently applicable value because it does not require complex surgical techniques and is easily accessible to those with relatively little surgical experience.

CONCLUSION

Among patients fixed with PFNA for treatment of unstable intertrochanteric fractures, less blade sliding and varus collapse was observed with geneX® ds augmentation compared to patients without it. In addition, the incidence of complications did not increase. The authors believe it can be regarded as a safe and effective additive for intramedullary fixation for treatment of unstable intertrochanteric fractures.

CONFLICT OF INTEREST

The authors declare that there is no potential conflict of interest relevant to this article.

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