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Efficacy of contained metaphyseal and periarticular defects treated with two different demineralized bone matrix allografts

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Abstract The efficacies of two different allografts, Grafton (demineralized bone matrix [DBM] in a glycerol carrier) and Orthoblast (DBM in a reverse thermal poloxamer carrier) were examined from cases involving periarticular fractures. Demographic, perioperative, and outcome data for patients with periarticular fractures who underwent a prospectively designed protocol for bone grafting were compiled, with 15 cases using Orthoblast and 13 using Grafton. A successful graft was defined as healing on the first graft attempt without complications. Healing was determined by radiographic studies and clinical evaluation. The successful graft rates of Orthoblast and Grafton were 15/15 and 9/13, respectively.

Résumé L'efficacité de deux allogreffes différentes, Grafton (Matrice osseuse déminéralisée [DBM] dans un porteur au glycérol) et Orthoblast (DBM dans un porteur au poloxamer) a été étudiée dans des cas de fractures périarticulaires. Les données démographiques, périopératoires, et évolutives chez des patients qui ont eu un protocole prospectif d'utilisation de ces allogreffes ont été compilées, avec 15 cas d'Orthoblast et 13 cas de Grafton. Un succès a été défini par une consolidation suivant la première tentative de greffe, sans complications. La consolidation a été déterminée par des études radiographiques et l'évaluation clinique. Les taux de succès des greffes Orthoblast et Grafton étaient de 15/15 et 9/13, respectivement.

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Introduction

Autogenous cancellous bone grafts have been the gold standard in reconstructive orthopedic surgery to repair fractures [9]. While these autografts show optimum skeletal incorporation and a low major complication rate, a postoperative minor complication rate as high as 35% and other intraoperative morbidities have been documented [21, 27]. Specifically, the disadvantages of iliac crest bone grafts have included postoperative complications (infection, wound drainage, hematomas, reoperation, chronic or prolonged pain, sensory loss, keloids, bowel herniation, and late fractures), and intraoperative complications (injury to the superior gluteal nerves or superior gluteal artery, sacroiliac joint and pelvic instability, ureteral injury, arteriovenous fistula, common peroneal and sciatic nerve palsy, and pelvic fracture) [2, 5, 21, 22, 27]. In addition, surgical morbidity at the second operation site limits the availability of graft, prolongs hospital stay, and increases costs [9, 21].

Hence, allografts (consisting of demineralized bone matrix [DBM], which provides the cellular elements for osteogenesis) and synthetic bone grafts (consisting of osteoconductive calcium phosphates, calcium sulfates and recombinant osteoinductive proteins) have been explored as alternative bone grafts [12, 21]. Although allografts combining both osteoconductive properties (using lyophilized, cancellous allogenic chips) and osteoinductive properties (using DBM) have been shown to be efficacious, [11, 13, 14, 15, 24] a rigorous clinical study evaluating the performance of allografts from different manufacturers has yet to be done. The purpose of this study was to examine the performance of two commercially available bone graft alternatives – Grafton (Osteotech, Eatontown, NJ, USA) and Orthoblast (Gensci, Irvine, CA, USA) – used in cases of periarticular fractures. This type of fracture poses special challenges for reconstructive surgical repair because of the high morbidity rate if joint salvage is not obtained [4].

Table 1 Comparison of demographics and outcomes of patients treated with Grafton or Orthoblast demineralized bone matrix allograft (MVA motor vehicle accident, MCA motor car accident)

	Grafton group No. (%)	Orthoblast group No. (%)
Total sites	13	15
Healing rate	9/13 (69)	15/15 (100)
Average age ($\pm$ SD)	39 $\pm$ 15.3 years	48 $\pm$ 15.5 years
Age range	15–69 years	24–77 years
Gender:		
Male	9 (69)	13 (87)
Female	4 (31)	2 (13)
Cause of injury:		
Fall	8 (62)	7 (47)
MVA/MCA	4 (31)	7 (47)
Industrial (falling objects)		1 (7)
Unknown	1 (8)	
Fracture site:		
Tibia/fibula	6 (46)	7 (47)
Femur	2 (15)	1 (7)
Humerus	3 (23)	
Forearm	2 (15)	1 (7)
Acetabulum		6 (40)
Smokers (more than ten cigarettes per day)	6 (46)	3 (20)
Significant comorbidities that affect healing:		
Coronary vascular disease	1 (8)	1 (7)
Diabetes		1 (7)
Hypothyroidism		1 (7) (Chronic obstructive pulmonary disease)
Other		1 (7) (Hodgkin's lymphoma)

Methods

This study utilized two consecutive series of patients with periarticular fractures who underwent a prospectively designed protocol for bone grafting. The first series used Grafton bone graft exclusively; after 3 years, a second series of new patients was treated with Orthoblast bone graft exclusively. All patients were treated by the senior author at the same tertiary care institution by the same surgeon employing a standardized technique, eliminating any variation due to different techniques from multiple surgeons. Patient's medical records were reviewed for demographic data (age, gender, smoking more than ten cigarettes per day), perioperative data (cause of injury, type of fixation, injury site, comorbidities), and outcomes of the surgical procedure. There were 15 cases using Orthoblast and 13 cases using Grafton. The inclusion criteria consisted of metaphyseal and periarticular fractures that required bone graft to fill defects or support loose joint pieces (or a combination) for proper reduction and fixation. All graft sites were contained defects, defined as a defect in which greater than 75% of the volume was surrounded by intact viable bone. Exclusion criteria consisted of patients who used electrical stimulators, those with diaphyseal fractures, frank bone loss, and infected sites. Screening consisted of sedimentation rate and C-reactive protein, and a technetium-indium bone scan, if needed. All patients had some type of internal fixation, followed by grafting. The composite graft was created by mixing cancellous bone chips (Lifenet, Virginia Beach, VA, USA) with either Orthoblast or Grafton DBM in a four to one ratio by volume. The amount of graft material used varied but was sufficient to bridge the affected area. Intraoperative cultures were not routinely taken, and wound drains were not used. Physiotherapy with non-weight bearing was instituted postoperatively. The mean follow-up time was 12 months. Healing was evaluated radiographically (bridging bone, evidence of remodeling, lack of hardware loosening) and clinically (painless weight bearing) by the senior author. A successful graft was de-

fined as healing on the first graft attempt without complications or a subsequent regraft. Failure was defined as any hardware or construct failure, persistent radiographic lucency, pain with weight bearing, or late collapse of graft. Statistical analysis was done using Fisher's exact test, with a P value <0.05 defined as statistically significant.

Results

As a combined group, patients treated with either Grafton or Orthoblast, 24 of the total 28 sites (86%) healed on the first attempt (Table 1). The group treated with Orthoblast consisted of 15 sites from 15 patients, with a mean age of 48 (SD $\pm$ 15.5, range 24–77) years. There were 13 men and two women. Cause of initial injury was motor vehicle accident/motor car accident (MVA/MCA) in seven, a fall in seven, and an industrial crushing object in one. There were seven cases involving the tibia or fibula, one involving the femur, six involving the acetabulum, and one involving the forearm. Eight patients had no systemic comorbidities; the other seven had comorbidities including diabetes, coronary artery disease, chronic obstructive pulmonary disease, Hodgkin's lymphoma, and hypothyroidism. In addition, three patients smoked more than ten cigarettes per day. All 15 patients healed successfully on the first graft attempt.

The group treated with Grafton consisted of 13 sites from 12 patients (one patient had two graft sites) with a mean age of 39 (SD $\pm$ 15.3, range 15–69) years. There

were nine men and four women. Cause of initial injury was an MVA/MCA in four, a fall in eight, and unknown in one. Six cases involved the tibia, two the femur, three the humerus, and two the forearm. Twelve patients had no systemic comorbidities; one had diabetes. In addition, six patients smoked more than ten cigarettes per day. As a subgroup, nine of 13 patients healed on the first attempt. All four patients who failed were smokers, of whom three were successfully grafted on the second attempt (two with Grafton and one with iliac crest autograft). The fourth patient who failed both smoked and had diabetes; the graft site went on to nonunion and became avascular, requiring total knee arthroplasty.

The greater success rate of Orthoblast was statistically significant (two-tailed $P=0.035$, likelihood ratio=6.918), with the probability of making a type 1 error set at 5% by convention ($\alpha=0.05$). A power analysis revealed that the chance of making a type 2 error was 39% ($\beta=0.39$). Estimates indicate that an additional six patients in the Orthoblast group or 15 in the Grafton group would be required to achieve $\beta<0.20$.

Discussion

An optimum bone graft should have two properties: (1) osteoconduction – a physical scaffold, such as collagen, that can facilitate the ingrowth and proliferation of osteoblasts, thus allowing new bone to grow from an adjacent osseous bed; and (2) osteoinduction – providing growth factors like BMP-2, BMP-4, BMP-7 and TGF- β , which induce undifferentiated mesenchymal cells to differentiate into osteoprogenitor cells [1, 28]. Since cancellous bone (ilium) is more osteoinductive than cortical bone (femur), the osteogenic progenitor cells used for autograft are most commonly harvested from the posterior iliac crest [19]. On the other hand, conventional mineralized allografts are mostly osteoconductive, in contrast to DBM that has both osteoconductive and osteoinductive activity [21].

This study demonstrated that periarticular fractures and other osseous defects treated with allograft and DBM have a favorable success rate comparable to pelvic autograft while at the same time avoiding the numerous donor site postoperative morbidities. Both Orthoblast and Grafton allografts were used to fill defects in periarticular fractures and additionally to support loose joint pieces for proper reduction and fixation [4]. Although treatment of periarticular fractures through open reduction and internal plate fixation is a common technique, it may cause extensive dissection and exposure, leading to tissue devitalization and further nonunion [6]. While minimally invasive fixation techniques such as percutaneous plating or external hybrid fixation devices avoid the disadvantages of open reduction and internal plate fixation, frequent infections from pin tracts, as well as complicated fractures with some bone loss, ultimately may still necessitate open reduction with bone grafting [10]. Unfortunately, despite uneventful fracture healing,

soft tissue swelling from edema and hemorrhage, combined with immobilization [8], can lead to progressive, if not permanent, joint stiffness via mechanisms still not fully characterized [16, 17, 23].

Examining two different types of commercially available allograft DBMs reveals that treatments with Orthoblast were significantly better ($P=0.035$) than treatments with Grafton for periarticular defects, as determined using Fisher's exact test method of statistical analysis. This test was used instead of Chi-square to compare the two groups because the former method is more accurate for smaller sample sizes. The reason for the observed difference in performance between Grafton and Orthoblast could be due to the intrinsic differences in osteoconduction and osteoinduction between the two allografts, especially since a major difference between them lies in the structural carrier used to deliver the DBM proteins. Grafton consists of DBM made up of insoluble collagen and proteins from ground or milled human bone, demineralized in dilute acid, rinsed with water, soaked in ethanol, and finally mixed with a glycerol carrier to form a gel-like consistency [19]. On the other hand, Orthoblast incorporates DBM with a reverse thermal poloxamer carrier. When dissolved in water at low ambient temperatures, poloxamer is a fluid liquid (sol) but at higher body temperatures, it forms a viscous liquid (gel). This property facilitates the retention and slow release of DBM and growth factors at the surgical site, which could enhance osteoinduction [7]. These differences in physical DBM carriers could be manifested when these grafts are used to fill periarticular fractures. Because the bony defects to be filled are acute contained, the lower mechanical stress, increased stability, and greater amount of healthy bone surrounding the graft (as compared to frank nonunions and other acute uncontained fractures) may have an impact on the osteoinductive and osteoconductive properties of the graft. This may subsequently lead to the difference in healing rates between Grafton and Orthoblast.

There were some dissimilarities between the groups that potentially could confound the reported results. The paucity of scientific data regarding such comorbidities (smoking, systemic disease, age, etc.) makes it difficult to draw any useful conclusion in this regard. Nonetheless, we have not identified any other studies that compare the performances of two bone graft substitutes. It has been widely documented that both tobacco usage and diabetes independently cause impaired bone healing and complications [1, 3, 18, 20, 25, 26]. Of the patients who failed using Grafton, each had these higher risk factors for failure. These factors were tobacco use alone (three sites) and tobacco use along with diabetes (one site). It should be noted that the Orthoblast group included only three smokers while the Grafton group included six, placing the entire Grafton group at a higher risk for failure. On the other hand, the Orthoblast group included more patients with significant comorbidities than the Grafton group. There was also an age gap between the two groups, although the older mean age of the Orthoblast group would predispose them to have a lower rather than higher healing rate.

A matched case series study and a larger sample size would reduce some of the confounding variables. Using this present study, we found the statistical power was 61%; this is lower than the optimum power of 80% in most large trials, where the sample size is large enough to have an 80% chance of detecting a statistically significant difference between the two groups of interest. Despite the reduced power, the results reject the null hypothesis that both allografts perform similarly. However, until larger studies are done comparing the performance of various allografts, the authors suggest caution about drawing any firm conclusions regarding the superiority of one commercial allograft versus another. Still, the observed difference between the success rates warrants further investigation on the performances of other brands. Taken as a combined group, these results demonstrate that overall allografts and DBM remain favorable alternatives to iliac crest bone graft.

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