

## Function After Injection of Benign Bone Lesions with a Bioceramic

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### Abstract

**Background** A novel calcium sulfate–calcium phosphate composite injectable bone graft substitute has been approved by the FDA for filling bone defects in a nonweightbearing application based on preclinical studies. Its utility has not been documented in the literature.

**Questions/purposes** We therefore determined postoperative function and complications in patients with benign bone lesions treated with this bioceramic.

**Methods** We retrospectively reviewed all 56 patients with benign bone lesions treated with the bioceramic from 2006 to 2008. There were 29 male and 27 female patients with an average age of 17.6 years (range, 4–63 years). They were treated for the following diagnoses: unicameral bone cyst (13), aneurysmal bone cyst (10), nonossifying fibroma (eight), fibrous dysplasia (five), enchondroma (four), chondroblastoma (four), and other (12). We obtained a Musculoskeletal

Tumor Society (MSTS) functional evaluation on all patients. The minimum followup was 26 months (average, 42 months; range, 26–57 months).

**Results** The average MSTS score was 29 (range, 20–30). Most patients returned to normal function. There were three local recurrences, all of which were treated with repeat injection or curettage. Two patients had postoperative fractures treated in a closed manner. Two patients had wound complications, neither of which required removal of the graft material.

**Conclusion** Patients treated with this material reported high MSTS functional scores more than 24 months after operative intervention and experienced low complication rates. We believe the novel bioceramic to be a reasonable treatment option for benign bone lesions.

**Level of Evidence** Level IV, therapeutic study. See Guidelines for Authors for a complete description of levels of evidence.

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### Introduction

Benign bone tumors and cysts are relatively common entities encountered in a general orthopaedic and orthopaedic oncology practice. This broad category encompasses lesions with widely varying clinical behaviors and natural histories. Treatment, therefore, must be individualized based on factors such as the specific tissue diagnosis, the size of the lesion, location of the lesion, associated symptoms, risk of pathologic fracture, and individual patient characteristics.

Traditionally, the autogenous bone graft has been the gold standard for all grafting procedures [16, 32]. Limited supply and substantial donor site morbidity, however, make this option less desirable [2, 3, 8, 10, 12, 13, 23, 26, 28]. Bone graft substitutes composed of calcium sulfate (CaSO<sub>4</sub>) or

calcium phosphate (CaPO<sub>4</sub>) are reasonable alternatives because they are biodegradable [16, 21, 32] and osteoconductive [16, 21, 32]. Furthermore, they do not contain potent cytokines [16, 21, 32], which may be contraindicated in the presence of tumors. In a selective review, Rougraff documented the limited published data on the use of bone graft substitutes in orthopaedic oncology [24]. Most reported series using surgical-grade CaSO<sub>4</sub> [16, 17, 20, 22] or CaPO<sub>4</sub> [21] graft materials to treat patients with benign bone tumors are relatively small with short followup. While various bone graft substitutes may be used to treat bone lesions, common complications still exist [16, 17, 20, 21, 24]. One of the major factors in determining the quality of bone graft substitutes is the rate of graft incorporation into the host bone. Histologic assessment offers effective evaluation of the rate of graft incorporation but is considered impractical given the requirement of the patient to undergo an additional procedure for a bone biopsy [27]. The alternative to histologic analysis is radiographic assessment; however, the literature lacks defined standardized assessment guidelines for radiographic investigation of bone graft incorporation [27].

Recently, an injectable CaSO<sub>4</sub>-CaPO<sub>4</sub> composite graft material with high compressive strength but an intermediate degradation profile has become available [32]. A preclinical canine study showed this material to be superior to CaSO<sub>4</sub> regarding the quantity and quality of bone formed in a contained humeral defect [30–32]. This material incorporates a matrix of CaSO<sub>4</sub> and dicalcium phosphate dihydrate (DCPD) into which β-tricalcium phosphate (β-TCP) granules are distributed [32]. The resorption profile is triphasic. The CaSO<sub>4</sub> resorbs first through simple dissolution, leaving behind an open-pore structure that allows for vascular infiltration and new bone deposition on the remaining CaPO<sub>4</sub> scaffold. DCPD has an intermediate profile [32], resorbing by osteoclastic resorption and simple dissolution. Finally, β-TCP only undergoes osteoclastic resorption and thus is retained longest.

We present the first clinical report of the novel injectable CaSO<sub>4</sub>-CaPO<sub>4</sub> composite graft material and specifically determined (1) the MSTS functional scores and the rates of (2) complications and (3) recurrences.

**Patients and Methods**

We retrospectively reviewed all 56 patients with benign bone tumors and cysts who underwent open curettage and débridement and filling with an injectable bone graft substitute, PRO-DENSE® (Wright Medical Technology, Arlington, TN, USA) from 2006 to 2008. The indications for surgery in this study are benign bone tumors that are thought to need surgery because of their potential biology

or risk of bone fracture thus leading to a contained osseous defect in a nonweightbearing clinical application. Latent stage 1 benign bone tumors were not treated and instead observed, but active (stage 2) and aggressive stage 3 benign bone tumors were routinely treated. The contraindications were: severe vascular or neurologic disease, uncontrolled diabetes, severe degenerative bone disease, closed bone void/gap filler, pregnancy, uncooperative patients who will not or cannot follow postoperative instructions including individuals who abuse drugs and/or alcohol, patients with hypercalcemia, patients with renal compromise, patients with a history of or active Pott’s disease, and patients with malignant tumors, segmental defects in long bone, and defects that require immediate postoperative weightbearing. This material was used in a consecutive series of patients who met the inclusion criteria. There were 29 male patients and 27 female patients. Their average age was 17.6 years (range, 4–63 years). Diagnoses included unicameral bone cyst (13), aneurysmal bone cyst (10), nonossifying fibroma (eight), fibrous dysplasia (five), enchondroma (four), chondroblastoma (four), and other (12), with 24 of the lesions located in the upper extremity and 32 located in the lower extremity (Table 1). The most common tumor or cyst locations were the humerus (15), femur (10), tibia (10), fibula (four), and other (17) (Table 2). Of the 56 patients, 10 were lost to followup and were unable to be contacted, leaving 46 patients.

**Table 1.** Patient diagnoses

Diagnoses	Number upper limb	Number lower limb	Total number
Unicameral bone cyst	9	4	13
Aneurysmal bone cyst	4	6	10
Nonossifying fibroma	0	8	8
Fibrous dysplasia	4	1	5
Enchondroma	1	3	4
Chondroblastoma	1	3	4
Other	5	7	12
Total	24	32	56

**Table 2.** Bone lesion location

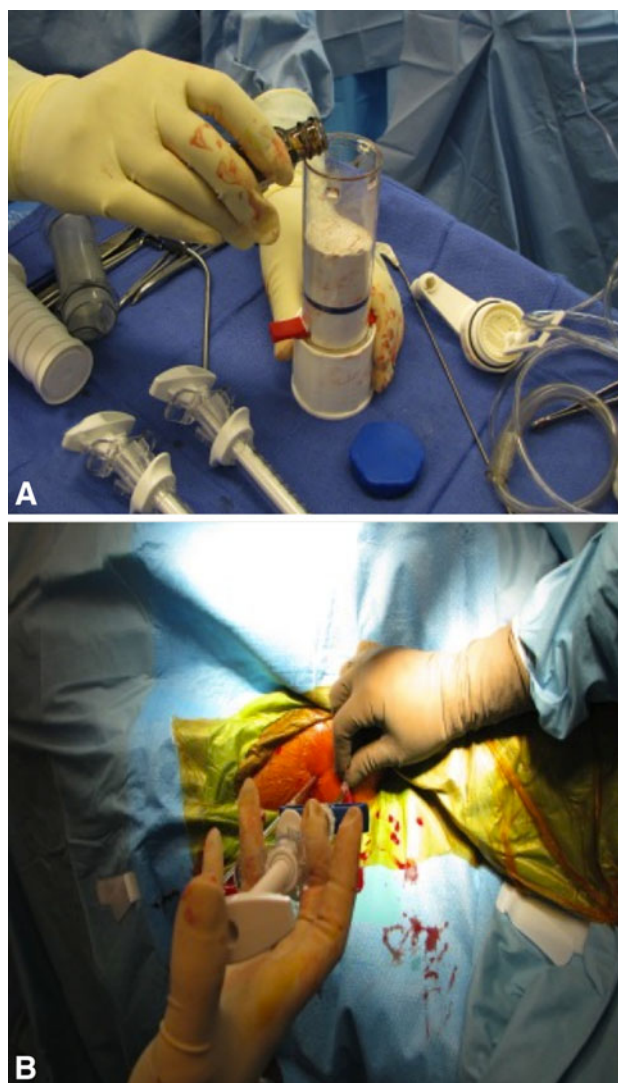
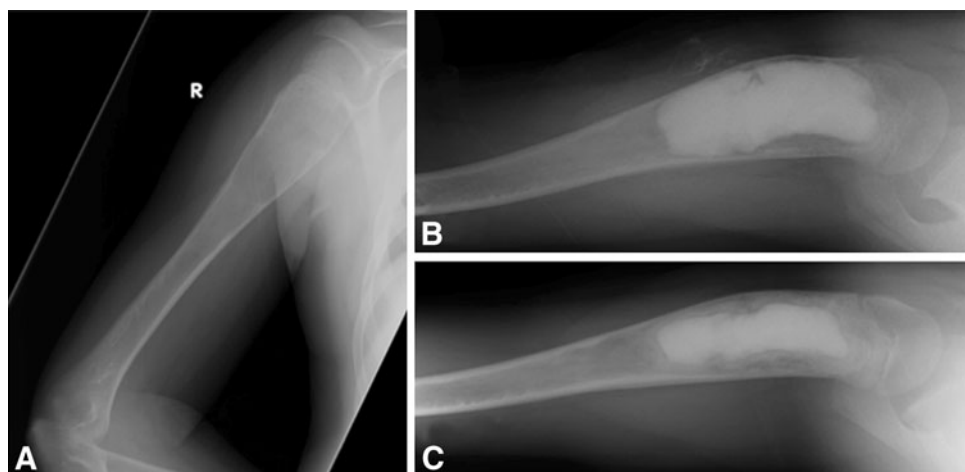
Location	Number
Humerus	15
Femur	10
Tibia	10
Fibula	4
Other	17
Total	56

The minimum followup was 26 months (average, 42 months; range, 26–57 months). This study was approved by the Institutional Review Board.

All patients were treated by one surgeon (SG). Thirteen lesions were treated with a percutaneous technique and 43 with open curettage. A percutaneous two-needle technique was used for diagnosis and treatment of unicameral bone cysts (Fig. 1); all other lesions were treated by an open approach. The lesion underwent biopsy and diagnosis was made by frozen section. The unicameral bone cysts were débrided through two 4-mm cannulas and then copiously lavaged after which PRO-DENSE<sup>®</sup> was injected through one cannula while using the other as a vent. The graft was prepared intraoperatively by mixing the powdered graft materials with aqueous diluents (Fig. 2A). The resulting composite is injectable for approximately 5 minutes and sets up in 20 to 30 minutes (Fig. 2B). Fluoroscopy was used to confirm that the entire cavity was filled. For open curettage, a longitudinal incision was made and a power burr used to create a cortical window. A biopsy specimen was taken and frozen section was performed. Curettes and elevators were used to remove lesional tissue. A power burr also was used to enlarge the tumor cavity. The tumor cavity then was irrigated with saline, dried, and filled with PRO-DENSE<sup>®</sup> (Fig. 3A). Postoperatively patients with lower extremity lesions were instructed to have protected weightbearing with the use of crutches for 8 weeks and patients with upper extremity lesions were instructed to avoid lifting objects for 8 weeks.

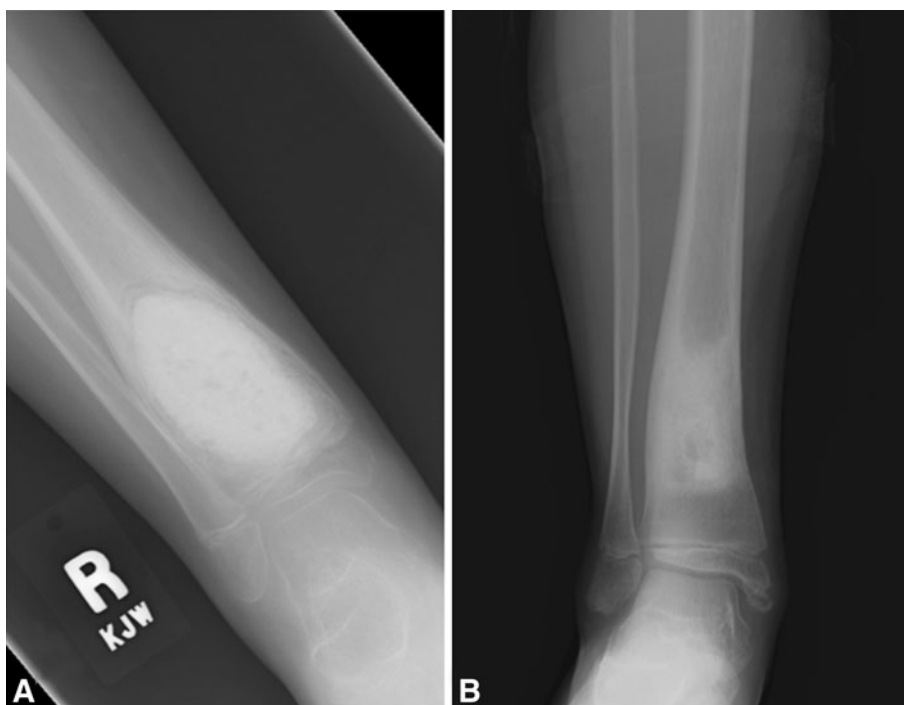
After discharge from the hospital, usually on an outpatient basis, the patients were followed in the clinic at intervals of 1 week and 1, 6, 12, and 18 months. The intervals were altered at the surgeon's discretion owing to variable healing rates and encountered complications. Each routine followup in the clinic included assessment of strength, ROM, functional status, and radiographic investigation to evaluate for potential fracture and presence of bone graft substitute (Figs. 1B–C, 3B).

**Fig. 1A–C** (A) A preoperative radiograph shows a unicameral bone cyst in a 12-year-old boy. (B) A 1-month postoperative radiograph after percutaneous injection of PRO-DENSE<sup>®</sup> graft material is shown. (C) The 2-month postoperative radiograph shows ceramic degradation and bone formation.



**Fig. 2A–B** (A) The graft is prepared intraoperatively on the back table by mixing the powdered graft materials with an aqueous diluent. (B) The resulting composite then is injected into the lesion through a cannula with a separate cannula used as a vent. The graft is injectable for approximately 5 minutes and sets up in 20 to 30 minutes.

**Fig. 3A–B** (A) A postoperative radiograph is shown after open curettage and grafting of a distal tibial aneurysmal bone cyst in a 13-year-old girl. (B) A radiograph obtained 1 year after surgery shows degradation of the ceramic and bony remodeling.



We used the MSTS functional evaluation system to assess function [9]; the information required was obtained from patients through a survey during the period between January and May 2011. We obtained a completed MSTS functional evaluation from all patients who were not lost to followup. This survey consists of a list of qualitative responses for multiple categories associated with a graded, numerical score for the upper and lower limbs. In the lower limb, the survey evaluates emotional acceptance; supports including brace, prosthesis, cane, or crutches; walking ability; and gait. In the upper limb, the survey evaluates function, emotional acceptance, hand positioning, dexterity, and lifting ability. Each category is rated from zero to five with a maximum total score of 30.

## Results

The average MSTS functional evaluation score was 29 (range, 20–30). The average score for patients with lower limb lesions was 29. The average for patients with upper limb lesions was slightly less at 28. The lowest score was 20 in a 32-year-old man with fibrous dysplasia of the humerus at 31 months followup. Twenty-three patients reported a perfect score of 30, eight of whom had upper limb lesions and 15 who had lower limb lesions.

Two patients (4%) had postoperative fractures. A 15-year-old boy with a nonossifying fibroma of the humerus sustained a fracture through his lesion 2 months postoperatively while playing soccer. This was treated with closed

reduction and casting. He returned to full activity and went on to play two sports in college. The second fracture occurred in a 22-year-old woman with an enchondroma of the proximal phalanx of the fifth toe. All fractures healed with nonoperative treatment. Two patients (4%) had postoperative wound complications. The first was a 17-year-old boy who underwent curettage of a distal femur osteoid osteoma. He later had a superficial wound infection develop that was treated successfully with a 1-week course of oral antibiotics. Resolution was seen 1 month postoperatively. The other complication was in a 32-year-old man with fibrous dysplasia of the proximal humerus. He had a wound infection develop 1 month postoperatively requiring incision and drainage. He also was treated with a 7.5-week course of intravenous and oral antibiotics. He achieved full recovery without complications.

Three patients (7%) had local recurrences. A 14-year-old boy with a chondroblastoma of the proximal femur had a local recurrence 1 year postoperatively. He was treated with repeat curettage and grafting and was doing well at his most recent postoperative visit. A 43-year-old woman with a giant cell tumor of the proximal humerus had a local recurrence of tumor 6 months after the initial procedure. She later underwent repeat open curettage with bone autograft. The patient also was doing well at her last postoperative visit. The last recurrence was in a 9-year-old boy with a proximal humerus unicameral bone cyst who had a recurrence 1.5 years after his initial procedure. He later underwent repeat percutaneous treatment. He returned to full activity and now participates in hockey. One of the

13 patients with a unicameral bone cyst treated percutaneously underwent a second injection of PRO-DENSE<sup>®</sup> because of a local recurrence.

## Discussion

PRO-DENSE<sup>®</sup> is a FDA-approved composite bioceramic for use in a contained osseous defect in a nonweightbearing application. Although a preclinical study [32] was promising, the literature contains no clinical report of this novel biomaterial. We therefore performed a retrospective case series of 56 patients treated with PRO-DENSE<sup>®</sup> for benign bone lesions to determine (1) the MSTS functional scores and the rates of (2) complications and (3) recurrences.

We acknowledge several limitations to our study. First, this is a relatively small study with short-term followup at an average of 3.5 years. Long-term followup is required to more adequately evaluate graft incorporation and bone remodeling. Second, this patient population is heterogeneous, including patients with multiple diagnoses of benign tumors and treated with percutaneous and open techniques. Owing to the small number of subjects in the study, comparison via surgical technique or diagnosis was deemed unreliable. Third, we did not assess radiographic incorporation of graft substitute owing to the lack of defined standardized assessment guidelines for radiographic investigation of bone graft incorporation.

The patients in our study achieved an average of 97% of that expected for normal function based on the observed average MSTS functional evaluation score of 29. Unfortunately only a limited number of studies could be identified in the literature that investigated the MSTS functional evaluation of bone graft and bone graft substitutes in the treatment of benign bone lesions (Table 3) [1, 11, 14, 16, 27]. Aho et al. [1] presented a study of 24 patients with benign bone lesions treated with an allograft who had an average MSTS functional evaluation of 83% with an average followup of 6 years. Gitelis et al. [11] reported on 23 patients with an average followup of 21 months who were treated with calcium sulfate for benign bone lesions and had an average MSTS functional evaluation of 98%. Hirata et al. [14] reported observations on 53 patients treated with  $\beta$ -TCP for benign bone lesions who had an average MSTS functional evaluation of 100%. Kelly and Wilkins [16] presented a study of 15 patients with benign bone lesions treated with calcium sulfate who had an average MSTS functional evaluation of 83% with an average followup of 6 months. Schindler et al. [27] reported findings for 13 patients treated with a composite ceramic bone graft substitute containing calcium sulfate and hydroxyapatite for benign bone tumors who had an

**Table 3.** Literature comparison of functional outcomes in bone graft studies

Study	Type of bone graft	Number of patients	Duration of followup	MSTS functional evaluation score*	Infection	Postoperative fracture	Local recurrence
Aho et al. [1]	Allograft	24	72 months	83%	4%	29%	0%
Gitelis et al. [11]	Calcium sulfate	23	21 months	98%	0%	4%	0%
Hirata et al. [14]	Tricalcium phosphate	53	NR	100%	0%	0%	4%
Kelly & Wilkins [16]	Calcium sulfate	15	6 months	83%	7%	7%	NR
Schindler et al. [27]	Calcium sulfate and hydroxyapatite	13	41 months	96%	NR	8%	15%
Current study	PRO-DENSE <sup>®</sup>	46	42 months	97%	4%	4%	7%

NR = not reported; \*MSTS functional evaluation scores reported as a percentage of the perfect score of 30 points.

average MSTS functional evaluation of 96% with an average followup of 41 months.

Complications in our patients were infrequent and in most cases likely were not attributable to the graft material. Two patients sustained postoperative fractures that healed with nonoperative treatment, and two experienced wound complications that did not require removal of the graft material. There were no other complications. This is comparable to other reported series of CaSO<sub>4</sub> and CaPO<sub>4</sub> bone graft substitutes [11, 16, 17, 20–22, 24, 32]. Complications, specifically tissue reaction and chronic wound drainage, appear to be decreased in our series compared with other series of patients treated with CaSO<sub>4</sub> [16, 17, 20]. We hypothesized that the rapid dissolution profile of pure CaSO<sub>4</sub> contributes to this complication. Thus, as expected, a composite graft with an intermediate profile appears to lessen the severity of the tissue reaction and wound problems. Furthermore, although not specifically quantified in this study, the composite graft material appears to exhibit the expected intermediate resorption profile and is gradually replaced by host bone (Fig. 4). This is in contrast to patients treated with pure CaPO<sub>4</sub> bone graft substitutes in whom residual graft material can be seen for years postoperatively and possibly permanently [21, 24].

In the current series, three patients (7%) experienced local recurrence. Although the study was not intended to

investigate the rate of recurrence of unicameral bone cysts as compared with alternative modes of treatment, a lower recurrence rate after percutaneous treatment with PRO-DENSE® was observed compared with rates reported in the literature [4–7, 15, 18, 25, 29, 33]. One of the 13 patients (8%) with a unicameral bone cyst experienced a recurrence. Authors have reported multiple percutaneous methods of treating unicameral bone cysts, the most common of which include injections with steroids [4–6, 29, 33], autogenous bone marrow aspirates [5, 6, 19, 33], demineralized bone matrix [18], and combinations of these [7, 15, 25, 29]. Although most patients can be treated by percutaneous methods, recurrence rates after the initial injections in these series range from 11% to 77%. In the current series, however, only one of the 13 (8%) unicameral bone cysts treated percutaneously has required a second injection. The remainder appeared to have healed with one injection. Although it was not an intended outcome, PRO-DENSE® appears to result in a lower recurrence rate after percutaneous treatment as compared with alternative treatment modalities.

With this new material we found high functional scores and infrequent complications compared with the literature. Based on these observations we believe it is a reasonable alternative to autogenous bone graft. Further study is needed to quantify the amount and rate of bone formation and the rate of graft dissolution for this material and other comparable materials over longer clinical periods. In addition, further investigation is required into the lower recurrence rate of unicameral bone cysts treated percutaneously with PRO-DENSE®.

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**Fig. 4** A CT scan obtained 19 months after percutaneous injection of PRO-DENSE® graft material in the proximal humerus unicameral bone cyst of a 12-year-old boy (patient in figures 1A–C) shows full degradation of the ceramic material with complete bone repair.

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