Effectiveness of Ultraporous β-Tricalcium Phosphate (Vitoss) as Bone Graft Substitute for Cavitary Defects in Benign and Low-Grade Malignant Bone Tumors

Corey Van Hoff, MD, Julie Balch Samora, MD, MPH, PhD, Michael J. Griesser, MD, Martha K. Crist, RN, BSH, Thomas J. Scharschmidt, MD, and Joel L. Mayerson, MD

Abstract

We retrospectively evaluated healing with ultraporous β-tricalcium phosphate (β-TCP [Vitoss; Orthovida, Malvern, Pennsylvania]) bone graft in patients who underwent surgical excision or curettage of benign bone lesions subsequently filled with bone void filler. Twenty-nine patients were treated with curettage and ultraporous β-TCP morsels. Radiologic defect size at initial postoperative presentation and subsequent visits (minimum follow-up, 6 months) was evaluated. Results suggested that an ultraporous β-TCP synthetic bone graft is effective in managing bone voids. The vast majority of patients who undergo curettage for benign bone lesions can expect to have complete or near complete healing of these defects within 6 months of their surgical procedure with use of ultraporous β-TCP morsels.

Surgical management of some benign and low-grade malignant bone tumors involves lesion curettage and leaving the resultant defect empty (when filler is contraindicated, as in the presence of acute or chronic infection), or filling it with bone graft or synthetic bone void filler in an attempt to promote and accelerate healing.[1,2] Wishing to minimize healing time and restore intrinsic bone strength, most surgeons prefer to graft the defect. The goal of this surgery is to completely fill the defect with the graft to promote eventual bone growth into the cavity. Given their osteogenic, inductive, and conductive properties, autologous bone grafts have been the gold standard of management.[3] However, harvesting these grafts can lead to higher morbidity, including infections, hematomas, neurovascular injuries, wound healing problems, heterotopic bone formation, cosmetic deformities, pain, and prolonged anesthesia time.[4,5]

Cancellous or cortical bone allografts, which can be fresh-frozen or freeze-dried, are a successful alternative to autografts, as they have osteoconductive properties and provide comparable results.[6,7] Banked allograft bone, however, is slow to incorporate, has the potential for immunogenicity, and has been known to carry bacteria and viruses.[8-10] Tomford and colleagues[8] reported allograft infection rates as low as 1% based only on patients who had a positive culture from a preoperative allograft. However, they found an allograft infection rate of 3.6% when patients with a proven postoperative infection were included and a rate of 6.9% when all patients with postoperative infection were included. In a study performed in the United Kingdom,[11] patients who received banked femoral heads over 1 year were compared with patients who underwent autograft procedures. The banked allograft group had an infection rate of 12.2%, and the autograft group had a rate of 3.5%. Interestingly, the procedure failure rate was 50% when there was a postoperative infection but only 4.2% where there was no infection. The authors concluded that procedures using banked allograft bone have a higher infection risk and a higher failure rate.

Synthetic bone grafts are safer for patients because of no additional donor-site morbidity, no risk for disease transmission, less operating time, and unlimited availability. Calcium-based bone void fillers have long been used as bone graft.[12,13] They are osteoconductive and resorbed at varying rates, depending on their specific chemical and physical properties.

Vitoss (Orthovida, Malvern, Pennsylvania) is a synthetic, calcium-based bone graft expander made of ultraporous β-tricalcium phosphate (β-TCP), or $Ca_3(PO_4)_2$. This most porous of β-TCP bone fillers received US Food and Drug Administration clearance in December 2000.[14] Ultraporous β-TCP bone filler has properties of both macroporosity,

Dr. Van Hoff is Assistant Professor, Dr. Samora and Dr. Griesser are Resident Physicians, Ms. Crist is Nurse, and Dr. Scharschmidt is Assistant Professor, Department of Orthopaedics, Ohio State University Medical Center, Columbus, Ohio.

Dr. Mayerson is Associate Professor, Ohio State University Medical Center, Columbus, Ohio; Director of Musculoskeletal Oncology, Arthur James Cancer Hospital, Ohio State University, Columbus, Ohio; and Program Director, Orthopaedics Residency Program, and Co-Director, Bone Tumor Clinic, Nationwide Children's Hospital, Columbus, Ohio.

Address correspondence to: Thomas J. Scharschmidt, MD, Division of Musculoskeletal Oncology, 1st Floor, Arthur James Cancer Hospital, Ohio State University, 300 W 10th Ave, Columbus, OH 43210-1280 (tel, 614-293-4420; fax, 614-293-3747; e-mail, thomas.scharschmidt@osumc.edu).

Am J Orthop. 2012;41(1):20-23. Copyright Quadrant HealthCom Inc. 2012. All rights reserved.

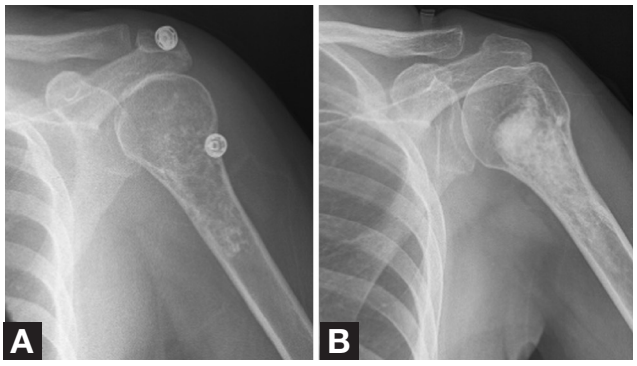

Figure 1. Representative preoperative (A) and 24-month postoperative (B) images of grade 2 filling defect of proximal humerus after curettage and filling with ultraporous β-tricalcium phosphate (Vitoss) morsels.

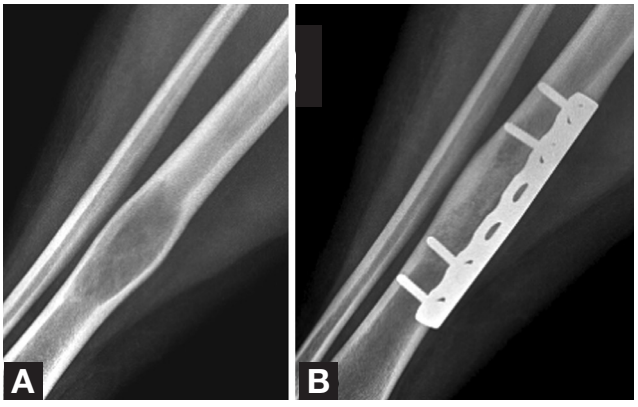

Figure 2. Representative preoperative (A) and 20-month postoperative (B) images after curettage and filling (with ultraporous β-tricalcium phosphate morsels) of tibial defect secondary to fibrous dysplasia. Defect is still apparent, but bony trabeculae traverse void. This is considered a grade 3 filling defect.

which allows for new bone appositional growth, and microporosity, which allows for fluid and nutrient transport. It is a highly biocompatible osteoconductive bone graft expander that facilitates trabecular bone formation.

We conducted a study to evaluate healing as demonstrated by radiographic resolution of benign bone tumors managed with ultraporous β-TCP and to determine whether ultraporous β-TCP is effective in managing bone voids in patients who undergo curettage for benign bone lesions.

Materials and Methods

This study was a retrospective, uncontrolled review of 29 consecutive patients with benign or low-grade malignant bone tumors. The senior author (J.L.M.) treated all patients with curettage and bone grafting using ultraporous β-TCP as a bone void filler without use of bone marrow aspirate. Additional hardware was used, depending on lesion size and location and presence or absence of pathologic fracture. All patients were followed clinically and radiographically for a minimum of 6 months; some patients had a 5-year follow-up. We obtained institutional review board approval before starting this review.

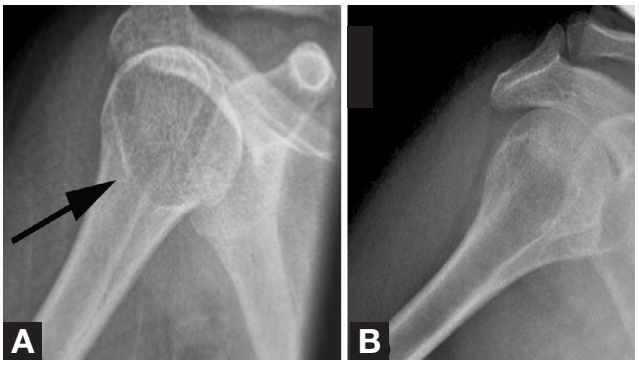

Figure 3. Representative preoperative (A) and 5-year postoperative (B) images of grade 4 filling defect (A, arrow) after curettage and filling of enchondroma with ultraporous β-tricalcium phosphate morsels. Defect is indistinguishable from surrounding bone (B).

Patients who underwent surgical excision or curettage of benign bone lesions that required a bone void filler were treated with ultraporous β-TCP morsels. Eighty-five patients who underwent surgery between January 1, 2003, and October 31, 2005, were evaluated. Preoperative and postoperative clinical and radiographic outcomes were assessed with outpatient medical records and orthopedic radiographs at 2 weeks to 6 weeks, 3 months, 6 months, and, if necessary, 12 months. Only those patients with a diagnosed bone tumor that required surgical management, including use of bone graft material, were included in the study (29 patients). Patients were excluded if they participated in another investigational drug or device trial, participated in a study that would interfere with the parameters being studied under this protocol, lacked preoperative imaging at our facility, were lost to follow-up, had no corresponding pathology, and used medication for osteoporosis (56 patients).

After curettage, each lesion underwent grafting with ultraporous β-TCP morsels without use of bone marrow aspirate. A special inserter was used to fill the defects. Packing was done manually, so as to fill the defects completely and without crushing the microporous superstructure. The dry ultraporous β-TCP mixture was gently packed into the defects and slightly overcompressed. Defect volume was calculated according to the methods of Damron.[14] All patients were followed clinically and radiographically for a mean (range) of 17.2 (6-34.5) months after surgery. Radiographs were obtained at each follow-up, and defect volume was calculated, thus permitting calculation of the proportion of the lesion healed at each time point. Defects were graded on a 4-point scale on the latest follow-up radiograph: grade 1 (lucency traversing entire defect space), grade 2 (lucency partly traversing entire defect space), grade 3 (trabeculae crossing entire defect space), and grade 4 (defect no longer distinguishable from surrounding bone).

Summary statistics for age, sex, initial lesion size, and length of follow-up were computed. To normalize the data across patients, we recorded an outcome measure of the proportion of the initial lesion healed at each follow-up.

Table. Patient Demographics

Age, y	Sex	Diagnosis	Location	Defect Size, mL
38	F	Enchondroma	Humerus	4.4×2.6×2.5 = 28.6
66	F	Enchondroma	Metatarsus	5.3×2.0×1.6 = 17.0
61	F	Unknown, benign	Femoral neck	4.0×3.7×2.3 = 34.0
48	F	Enchondroma	Humerus	11.5×3.2×3.8 = 139.8
45	F	Intraosseous lipoma	Calcaneus	2.2×2.4×2.2 = 11.6
43	F	Unicameral bone cyst	Tibia	5.1×3.7×3.8 = 71.7
59	F	Enchondroma	Femoral shaft	15.8×2.3×2.4 = 87.2
21	F	Nonossifying fibroma	Fibula	2.4×1.5×1.7 = 6.12
48	F	Unicameral bone cyst	Tibia	2.9×2.4×1.8 = 12.5
18	M	Nonossifying fibroma	Femur	6.3×4.2×4.4 = 116.4
16	M	Nonossifying fibroma	Femur	4.2×2.3×2.2 = 21.3
61	F	Low-grade cartilage lesion	Fibula	4.2×2.3×2.2 = 21.3
80	F	Enchondroma	Humerus	6.3×3.3×3.1 = 64.4
19	M	Chondroblastoma	Humerus	4.6×3.1×2.4 = 34.2
33	F	Enchondroma	Humerus	7.7×3.1×3.1 = 74.0
42	F	Enchondroma	Humerus	2.5×2.5×2.4 = 15.0
11	F	Aneurysmal bone cyst	Tibia	6.1×3.3×3.9 = 78.5
21	M	Eosinophilic granuloma	Femur	8.9×3.0×2.4 = 64.1
54	F	Low-grade cartilage lesion	Femur	4.7×3.1×2.5 = 36.4
17	M	Enchondroma	Humerus	3.2×2.1×2.5 = 16.8
48	F	Benign fibro-osseous lesion	Humerus	1.5×2.7×2.1 = 8.5
20	F	Unicameral bone cyst	Tibia	4.9×2.4×2.4 = 28.2
38	F	Enchondroma	Humerus	2.8×2.1×1.8 = 10.6
19	F	Lamellar and woven bone, benign	Tibia	5.9×3.8×3.3 = 74.0
17	M	Nonossifying fibroma	Humerus	3.2×2.1×1.5 = 10.1
16	M	Fibrous dysplasia	Femur	5.9×3.0×3.8 = 67.3
56	F	Low-grade chondrosarcoma	Femur	4.6×4.2×3.8 = 73.4
38	F	Low-grade chondrosarcoma	Femur	11.7×4.1×3.6 = 172.7
21	F	Fibrous dysplasia	Tibia	4.1×2.2×2.2 = 19.8

This proportion was logit-transformed to improve its linearity for statistical modeling. A mixed-effects model was used to describe the relationship between time and healing, which allowed for adjusting the correlation between measurements on the same patient and quantifying between- and within-patient variability. The covariates of age, sex, and initial lesion size were considered for inclusion in the model. Analyses were performed with SAS Version 9.1 (SAS Institute, Cary, North Carolina) and Stata Version 10.0 (StataCorp, College Station, Texas).

Results

There were 29 patients (22 women, 7 men) in our study cohort (Table). Mean (range) age was 36 (11-80) years. Fourteen patients had low-grade cartilage lesions, 4 had nonossifying fibromas, 2 had fibrous dysplasia, and 3 had unicameral bone cysts. One patient each was diagnosed with eosinophilic granuloma, intraosseous lipoma, chondroblastoma, and aneurysmal bone cyst. Pathology was undetermined, though benign, for 1 patient.

Ten lesions were located in the upper extremities (all in the humerus). The other 19 lesions were located in the lower extremities: 9 in the femur (including 1 in the femoral neck and 1 in the femoral shaft), 6 in the tibia, 2 in the fibula, and 1 each in the calcaneus and first metatarsal shaft.

Mean (range) defect volume was 48.8 (6.12-172) mL, and mean (range) follow-up was 17.1 (6-34.5) months. Mean (range) defect size at most recent follow-up was 18.7 (0-85.9) mL. There were no grade 1 defects, 1 grade 2 defect, 14 grade 3 defects, and 14 grade 4 defects (Figures 1–3).

Of the 29 patients, 25 mobilized on schedule and were clinically pain-free at 3-month follow-up. There were no infections. One patient was diagnosed by pathology and plain radiographs with an enchondroma of a metatarsus but was later found to have a chondrosarcoma, for which she underwent a below-knee amputation. One patient who underwent curettage for a benign lesion, likely avascular necrosis (AVN)—the pathology was not definitive—underwent core decompression after developing definitive radiographic evidence of AVN. One patient had a nonossifying fibroma of the proximal fibula recur and underwent repeat curettage, freezing, and grafting. One patient developed AVN of the femoral condyle and underwent total knee arthroplasty.

Discussion

After blood, bone graft is the most commonly transplanted tissue.[3] Bone grafts are used in managing fractures, infections, tumors, degenerative diseases, nonunions, periprosthetic bone loss, and fusions.[3,15] It is of utmost importance to determine the safest, most effective material to use for bone grafting.

Use of a void filler is successful when the defect is completely filled with bone of normal density and appearance and when no implant material remains. Any filling agent should be able to be contoured to the dimensions of the defect and should allow rapid ingrowth such that native bone can ultimately replace the graft material. Calcium phosphate ceramics are safe, have osteoconductive properties, lack allergenicity, and have strong bone-bonding capac-

ity. The advantages of synthetic bone graft over cancellous bone include increased patient safety, lack of donor-site morbidity, unlimited availability and shelf life, and reduced operating time.

Vitoss is a low-density, ultraporous matrix, based on nanoparticles (mean size, 100 nm) of TCP, that approximates the structure of native cancellous bone.[16] When implanted in direct contact with viable bone, ultraporous β-TCP facilitates new bone growth in 3 dimensions by serving as a scaffold. Because of its particle size, ultraporous β-TCP is resorbed mainly by cell-mediated processes. Its broad range of pore sizes allows migration, seeding, and retention of osteoblasts and osteoclasts while ensuring an unobstructed fluid flow for delivery of oxygen and nutrients.[17] Ultraporous β-TCP has properties of both macroporosity, which allows for new bone appositional growth, and microporosity, which allows for fluid and nutrient transport and infiltration by bone-forming cells and growth factors.[18] These factors allow for early formation and remodeling of bone throughout the scaffold and for almost complete resorption of the implant when new bone formation is completed.

β-TCP alone[19] and combined with bone marrow aspirate[20] has been shown to be safe and effective in the management of cavitary lesions. As there is very little information about time to resorption of synthetic bone grafts, it is difficult to compare remodeling and allograft. Knowing more about resorption timing could be beneficial in counseling patients and in advancing or restricting activities.

In this retrospective study, we assessed the clinical outcome of surgical management of benign bone tumors treated with ultraporous β-TCP morsels. Twenty-eight of the 29 patients treated with ultraporous β-TCP morsels had defects with trabeculae crossing the entire defect space or defects that were no longer distinguishable from surrounding bone. Resorption and trabeculation were noted to increase radiographically at each time point after surgery. Defect filling progressed steadily at all time points. As Anker and colleagues[19] also reported, resorption started peripherally and extended centrally. We also noted trabeculation through the central portion of the grafts, along lines of stress concentration. By 3 months, approximately 33% of each defect had progressed to resorption and trabeculation. By 6 months, roughly 50% had progressed to trabeculation.

This study had many limitations, including retrospective collection of data and lack of a control group. In addition, the grading system we used for the radiographic defects is not a validated tool. Defect volume was calculated according to the methods of Damron.[14] The lead author (C.V.) was the primary reviewer of radiographs, and all other authors (except the study's registered nurse [M.K.C.]) performed random assessments of obtained values; there was general agreement on the grading. The lead author's assessments were not blinded, but the other authors' assessments were.

Autogenous bone graft, with its osteoinductive, osteoconductive, and osteogenic properties, remains the gold standard for management. No other bone substitute has all 3 of these properties. However, biological/synthetic composite grafts are a promising emerging surgical option.[18]

Cost is a consideration when deciding which method to use to fill the bony void. Although autogenous grafting is the traditional gold standard, it has fallen out of favor in most cases because of the additional surgical procedure required and because of the increased pain and morbidity associated with it. Most clinicians now favor either allograft or a synthetic substitute. The list cost for 15 mL of allograft cancellous chips from the Musculoskeletal Transplant Foundation is $191, and the list cost for 15 mL of Vitoss is $1180. Obviously, the costs, advantages, and disadvantages of these products must be considered before making clinical decisions.

Ultraporous β-TCP is an efficacious, reliable, safe, readily available, and somewhat costly bone graft material. We can recommend it for benign and low-grade malignant bone tumors that require curettage and filling of cavitary defects. However, prospective, randomized studies comparing β-TCP with autologous bone graft and with synthetic composite bone grafts would aid in providing evidence that can be used to make informed clinical decisions.

Authors' Disclosure Statement

The authors report no actual or potential conflict of interest in relation to this article.

References

1. Greis PE, Hankin FM. Eosinophilic granuloma. The management of solitary lesions of bone. *Clin Orthop.* 1990;(257):204-211.
2. Mendenhall WM, Zlotecki RA, Scarborough MT, Gibbs CP, Mendenhall NP. Giant cell tumor of bone. *Am J Clin Oncol.* 2006;29(1):96-99.
3. Van Heest A, Swiontkowski M. Bone-graft substitutes. *Lancet.* 1999;353(suppl 1):S128-S129.
4. Younger EM, Chapman MW. Morbidity at bone graft donor sites. *J Orthop Trauma.* 1989;3(3):192-195.
5. Kurz LT, Garfin SR, Booth RE Jr. Harvesting autogenous iliac bone grafts. A review of complications and techniques. *Spine.* 1989;14(12):1324-1331.
6. Urist M, O'Connor B, Burwell R. *Bone Grafts, Derivatives and Substitutes.* Oxford, England: Butterworth Heinemann; 1994.
7. Glancy GL, Brugioni DJ, Eilert RE, Chang FM. Autograft versus allograft for benign lesions in children. *Clin Orthop.* 1991;(262):28-33.
8. Tomford WW, Starkweather RJ, Goldman MH. A study of the clinical incidence of infection in the use of banked allograft bone. *J Bone Joint Surg Am.* 1981;63(2):244-248.
9. Buck BE, Malinin TI, Brown MD. Bone transplantation and human immunodeficiency virus. An estimate of risk of acquired immunodeficiency syndrome (AIDS). *Clin Orthop.* 1989;(240):129-136.
10. An HS, Lynch K, Toth J. Prospective comparison of autograft vs. allograft for adult posterolateral lumbar spine fusion: differences among freeze-dried, frozen, and mixed grafts. *J Spinal Disord.* 1995;8(2):131-135.
11. Sutherland AG, Raafat A, Yates P, Hutchison JD. Infection associated with the use of allograft bone from the north east Scotland Bone Bank. *J Hosp Infect.* 1997;35(3):215-222.
12. Dreesman H. Über Knochenplombierung. *Beitr Klin Chir.* 1892;9:804-810.
13. Peltier LF, Jones RH. Treatment of unicameral bone cysts by curettage and packing with plaster-of-paris pellets. *J Bone Joint Surg Am.* 1978;60(6):820-822.
14. Damron TA. Use of 3D beta-tricalcium phosphate (Vitoss) scaffolds in repairing bone defects. *Nanomedicine (Lond).* 2007;2(6):763-775.
15. McGee P. Filling the void: current and future technology in bone grafting materials. *Orthopedics.* 1998;18:1.
16. Bucholz RW, Carlton A, Holmes R. Interporous hydroxyapatite as a bone graft substitute in tibial plateau fractures. *Clin Orthop.* 1989;(240):53-62.
17. Erbe EM, Marx JG, Clineff TD, Bellincampi LD. Potential of an ultraporous beta-tricalcium phosphate synthetic cancellous bone void filler and bone marrow aspirate composite graft. *Eur Spine J.* 2001;10(suppl 2):S141-S146.
18. Giannoudis PV, Dinopoulos H, Tsiridis E. Bone substitutes: an update. *Injury.* 2005;36(suppl 3):S20-S27.
19. Anker CJ, Holdridge SP, Baird B, Cohen H, Damron TA. Ultraporous beta-tricalcium phosphate is well incorporated in small cavitary defects. *Clin Orthop.* 2005;(434):251-257.
20. Siegel HJ, Baird RC III, Hall J, Lopez-Ben R, Lander PH. The outcome of composite bone graft substitute used to treat cavitary bone defects. *Orthopedics.* 2008;31(8):754.