Use of a Calcium Sulfate–Calcium Phosphate Synthetic Bone Graft Composite in the Surgical Management of Primary Bone Tumors

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abstract

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Benign primary bone tumors are commonly treated with intralesional curettage with or without the use of surgical adjuvants. The reconstructive approach to the resulting contained bone defects is controversial, and clinical practice is varied. Synthetic bone substitutes may provide early mechanical support while minimizing the risks of disease transmission, nonunion, infection, and donor-site morbidity. Limited data exists regarding the use of calcium sulfate–calcium phosphate composite bone substitute for this purpose.

The authors retrospectively reviewed the clinical outcomes of 24 patients with benign primary bone tumors who underwent intralesional curettage followed by reconstruction with a calcium sulfate–calcium phosphate composite bone substitute. Mean follow-up was 23 months. The most common diagnosis was giant cell tumor of bone. Six patients had upper-extremity tumors and 18 had lower-extremity tumors. Mean preoperative radiographic tumor volume was 41.0 cm³. Mean volume of PRO-DENSE (Wright Medical Technology, Arlington, Tennessee) used in each patient was 15.6 cm³. Mean time to full weight bearing for all patients was 7.3 weeks. Two patients sustained local tumor recurrences. No postoperative fractures occurred, and no complications occurred related to the use of the calcium sulfate–calcium phosphate composite. One case of deep infection occurred secondary to wound breakdown. The use of a calcium sulfate–calcium phosphate composite was associated with rapid biological integration and an early return to activities of daily living, with no composite-related complications.

This technique is a viable option in the reconstruction of cavitory bone defects following intralesional curettage of primary benign bone tumors.

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Benign primary bone tumors are commonly treated with intralesional curettage with or without the use of surgical adjuvants. In comparison with resection, these techniques minimize patient morbidity and surgical complexity while achieving comparable local recurrence rates. However, the reconstructive approach to the resulting contained bone defects is controversial, and clinical practice is varied.

Polymethylmethacrylate (PMMA) bone cement, allograft bone, and autograft bone have been used to fill bone defects after intralesional curettage of benign bone tumors. Polymethylmethacrylate does not preserve bone stock, and the hardened cement does not share the same biomechanical properties as bone. The risks of allograft are disease transmission, deep infection, and nonunion, and its biological properties vary after preparation. Autograft necessitates donor-site morbidity and is available in limited quantity. Some authors leave voids unfilled, but this may lead to early fracture or collapse.

To avoid these limitations, the use of synthetic bone substitutes is becoming increasingly popular. Synthetic bone substitutes eliminate the risk of disease transmission, obviate the possibility of donor-site morbidity, are processed to homogeneous particle sizes, are available in relatively limitless quantity, and may provide sufficient mechanical support to allow early functional rehabilitation. Whereas some synthetic bone substitutes are purely osteoconductive and provide a scaffold for gradual bony ingrowth, others are osteoinductive because they stimulate the rapid regeneration of host bone stock and biological reintegration.

PRO-DENSE (Wright Medical Technology, Arlington, Tennessee) is a fully synthetic bone substitute comprising a composite calcium sulfate–calcium phosphate (CaSO₄/CaPO₄) matrix mixed with beta-tricalcium phosphate (β-TCP) granules. The CaPO₄ component provides a robust scaffold for osteogenesis, whereas the CaSO₄ component resorbs rapidly to create porosity while stimulating bony ingrowth. In combination, CaSO₄ and CaPO₄ have promoted significantly more new host bone formation compared with autograft bone, CaSO₄ alone, or β-TCP alone.

Using PRO-DENSE to reconstruct cavitary bone defects after intralesional curettage of primary benign bone tumors is relatively new; the product became available within the past 10 years. The current authors recently published an outline of the chronology of the radiographic appearance of PRO-DENSE reconstruction following the resection of benign primary bone tumors in a small patient cohort. The current article describes a larger number of patients and their clinical outcomes, with particular emphasis on rapid biological regeneration and early functional recovery.

**MATERIALS AND METHODS**

This study received ethics approval from the McMaster University/Hamilton Health Sciences Research Ethics Board (REB# 12-388-C).

Using a surgeon-specific database, all patients who underwent intralesional curettage of a primary bone tumor followed by cavitary reconstruction with PRO-DENSE were identified. Patients who underwent PRO-DENSE reconstruction for indications other than a bone tumor and patients whose PRO-DENSE reconstruction was supplemented by internal fixation or other graft materials were excluded. Local institutional ethics approval was obtained to review patient records. Twenty-four patients met the inclusion criteria and were retrospectively reviewed.

All procedures were performed by 2 surgeons (M.G., B.D.) at 1 institution between July 2007 and July 2012. After clearly exposing each tumor, the neocortex was excised, and extended curettage was performed. When all gross tumor was removed, a high-speed burr was used to further debride the cavitary defect and to ensure complete tumor excision. Copious saline irrigation was used between several passes of the high-speed burr. The defect was then reconstructed by the direct injection of PRO-DENSE. Postreconstruction plain radiographs were obtained to confirm sufficient cavity filling. All patients were followed with a clinical examination and plain radiographs at 2 and 4 weeks postoperatively and then at 3-month intervals until 2 years after the index procedure. Subsequent follow-up occurred every 6 months. Activity restrictions were lifted when radiographic evidence existed of circumferential partial graft resorption and surrounding partial osseous ingrowth.

Clinical outcome data were extracted from electronic and paper medical records. Collected information included patient demographics (ie, age and sex), tumor location, radiographic tumor dimensions and calculated 3-dimensional volume, final pathologic diagnosis, and volume of PRO-DENSE used in each procedure. Time to partial and unrestricted full weight bearing, incidence of complications, tumor recurrence, and follow-up duration were also recorded. Partial weight bearing was defined as range of motion exercises in patients with upper-extremity tumors and at least 50% weight bearing in patients with lower-extremity tumors. Full weight bearing was defined as the resumption of all activities of daily living as tolerated with no imposed restrictions in patients with upper-extremity tumors and ambulation without assistive devices in patients with lower-extremity tumors. Radiographic dimensions (ie, craniocaudal, mediolateral, and anteroposterior) were obtained from preoperative magnetic resonance imaging studies, and 3-dimensional volumes were calculated. The relative proportion of PRO-DENSE required to fill each void as a percentage of the preoperative tumor volume were calculated using Microsoft Excel 2008 (Santa Rosa, California).

Twenty-four patients underwent intralesional curettage followed by bone void...
filling with PRO-DENSE between July 2007 and July 2012. Patient and tumor characteristics are summarized in Table 1. Twelve men and 12 women were included, with a mean age at surgery of 23.7 years (range, 9-64 years). Clinical follow-up ranged from 2 months to 4.5 years (mean, 23 months). The most common pathologic diagnosis was giant cell tumor of bone (n=7), followed by aneurysmal bone cyst (n=6), and enchondroma (n=3). Other tumor types included were unicameral bone cyst, chondroblastoma, low-grade chondrosarcoma, benign surface cartilaginous tumor, and simple bone cyst. Tumors were located in the upper extremity in 6 patients and in the lower extremity in 18 patients. Preoperative radiographic tumor volume ranged from 0.3 to 159.2 cm³ (mean, 41.0 cm³).

### RESULTS

In patients with upper-extremity tumors, mean time to partial weight bearing was 3.2 weeks and mean time to full weight bearing was 8.3 weeks. For patients with lower-extremity tumors, mean time to partial weight bearing was 3.4 weeks and mean time to full weight bearing was 6.9 weeks. Time in weeks to partial weight bearing and full weight bearing for all patients is shown in Table 2. Overall mean time to full weight bearing was 7.3 weeks. The volume of PRO-DENSE required to reconstruct each tumor ranged from 2.0 to 64.0 cm³ (mean, 15.6 cm³) (Table 2).

Two patients sustained local recurrences of their tumors. Patient 3’s proximal humeral giant cell tumor of bone recurred 14 months postoperatively. His original tumor volume was 92.9 cm³, and he received 30 cm³ of PRO-DENSE. He underwent subsequent en bloc excision with endoprosthetic reconstruction and was disease free 4 months later. Based on the stable imaging appearance over time but ongoing proximal tibia pain, patient 11 was clinically suspected to have a recurrence of her proximal tibia aneurysmal bone cyst 5 months postoperatively. Her original tumor volume was 27.9 cm³, and she received 14 cm³ of PRO-DENSE. She underwent repeat curettage and PRO-DENSE reconstruction, but final pathology confirmed that the tumor had not recurred but that the PRO-DENSE had not yet fully incorporated. She was disease free and asymptomatic 2 years later.

Patient 17 sustained a wound breakdown, which led to a deep surgical-site infection 13 weeks postoperatively. His proximal tibia giant cell tumor of bone tumor volume was 180 cm³, and he received 64 cm³ of PRO-DENSE. He underwent complete PRO-DENSE removal, extensive irrigation and debridement, and implantation of antibiotic-laden PMMA. Three months later, he was fully weight bearing, and his wound had healed.

### Table 1

<table>
<thead>
<tr>
<th>Patient No./ Sex/Age, y</th>
<th>Tumor Location</th>
<th>Pathologic Diagnosis</th>
<th>Tumor Volume, cm³</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/F/14</td>
<td>Tibia</td>
<td>UBC</td>
<td>36.5</td>
</tr>
<tr>
<td>2/F/14</td>
<td>Distal fibula</td>
<td>UBC</td>
<td>8.2</td>
</tr>
<tr>
<td>3/M/25</td>
<td>Humerus</td>
<td>GCT and ABC</td>
<td>92.9</td>
</tr>
<tr>
<td>4/M/24</td>
<td>Patella</td>
<td>ABC</td>
<td>14.9</td>
</tr>
<tr>
<td>5/M/17</td>
<td>Clavicle</td>
<td>ABC</td>
<td>24.8</td>
</tr>
<tr>
<td>6/F/43</td>
<td>Metatarsal</td>
<td>Enchondroma</td>
<td>0.3</td>
</tr>
<tr>
<td>7/M/31</td>
<td>Distal fibula</td>
<td>GCT</td>
<td>21.0</td>
</tr>
<tr>
<td>8/M/14</td>
<td>Proximal humerus</td>
<td>Chondroblastoma</td>
<td>16.9</td>
</tr>
<tr>
<td>9/M/64</td>
<td>Proximal pharynx (foot)</td>
<td>Enchondroma</td>
<td>2.7</td>
</tr>
<tr>
<td>10/F/33</td>
<td>Humerus</td>
<td>Enchondroma</td>
<td>14.9</td>
</tr>
<tr>
<td>11/F/18</td>
<td>Proximal tibia</td>
<td>ABC</td>
<td>27.9</td>
</tr>
<tr>
<td>12/F/53</td>
<td>Proximal tibia</td>
<td>Grade 1 chondrosarcoma</td>
<td>20.8</td>
</tr>
<tr>
<td>13/M/15</td>
<td>Proximal tibia</td>
<td>Chondroblastoma</td>
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<tr>
<td>14/M/13</td>
<td>Proximal femur</td>
<td>Chondroblastoma</td>
<td>7.1</td>
</tr>
<tr>
<td>15/F/56</td>
<td>Distal femur</td>
<td>GCT</td>
<td>159.2</td>
</tr>
<tr>
<td>16/M/27</td>
<td>Distal femur</td>
<td>GCT</td>
<td>108.2</td>
</tr>
<tr>
<td>17/M/28</td>
<td>Proximal tibia</td>
<td>GCT</td>
<td>180.2</td>
</tr>
<tr>
<td>18/F/21</td>
<td>Humerus</td>
<td>Benign surface cartilaginous tumor</td>
<td>4.4</td>
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<tr>
<td>19/M/9</td>
<td>Distal radius</td>
<td>ABC</td>
<td>39.1</td>
</tr>
<tr>
<td>20/F/47</td>
<td>Distal tibia</td>
<td>Recurrent GCT</td>
<td>29.8</td>
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<tr>
<td>21/F/16</td>
<td>Proximal tibia</td>
<td>GCT</td>
<td>31.3</td>
</tr>
<tr>
<td>22/F/15</td>
<td>Proximal femur</td>
<td>ABC</td>
<td>32.1</td>
</tr>
<tr>
<td>23/M/18</td>
<td>Femoral neck</td>
<td>Simple bone cyst</td>
<td>92.2</td>
</tr>
<tr>
<td>24/F/25</td>
<td>Femoral neck</td>
<td>Simple bone cyst</td>
<td>16.4</td>
</tr>
</tbody>
</table>

Abbreviations: ABC, aneurysmal bone cyst; GCT, giant cell tumor; UBC, unicameral bone cyst.
No cases of postoperative fracture occurred, and no complications occurred related to the use of PRO-DENSE. All reconstructions followed the previously described radiographic pattern of bone regeneration and consolidation. Partial resorption of the composite occurred as early as 2 weeks postoperatively and was visualized as a peripheral radiolucency surrounded by a circumferential shell of radiodense osseous integration that progressed inward centripetally. This pattern was used as a guide for advancing weight-bearing activities. Complete resorption and new bone incorporation typically occurred by 1 year postoperatively for larger defects (larger than 10 cm³) and by 3 to 6 months postoperatively for smaller defects (smaller than 10 cm³). Examples of the typical radiographic appearance and course are shown in Figures 1 and 2.

**DISCUSSION**

Using PRO-DENSE to reconstruct cavitory bone defects after intralesional curettage of primary benign bone tumors is relatively novel. In the current report, the authors added 13 patients to their previous radiology-focused report and examined the clinical implications of the rapid biological integration of PRO-DENSE on early functional recovery. Patients in the current study returned to full weight bearing and unrestricted activities of daily living at a mean of 7.3 weeks. No complications occurred related to the use of PRO-DENSE, and 2 local recurrences occurred.

The rapid biological integration and favorable mechanical properties of PRO-DENSE seem to be related to its synthetic composition. PRO-DENSE contains a matrix of CaSO₄/β-CaPO₄ embedded with β-TCP granules. Calcium sulphate resorbs significantly faster than the rate of new bone growth, leaving it unsuitable as a material scaffold to support early functional rehabilitation. In contrast, CaPO₄ supported early weight bearing
after the reconstruction of traumatic bone defects, but its slow rate of resorption and high density do not allow for rapid bone regeneration.\textsuperscript{15,16} When combined, \textit{CaPO}_4 slows the resorption of \textit{CaSO}_4 while the \textit{β}-TCP granules create a porous scaffold. This provides a biomechanically stable and osteoconductive environment for new bone formation. Although local growth factors stimulate angiogenesis and the recruitment of osteoblasts, \textit{CaPO}_4 may also be osteoinductive by activating the release of stimulatory proteins by the local scaffold.\textsuperscript{17} In animal studies, \textit{CaSO}_4 and \textit{CaPO}_4 composites promoted significantly more new host bone formation compared with autograft bone, \textit{CaSO}_4 alone, or \textit{β}-TCP alone.\textsuperscript{5,11,12}

Notable advantages are associated with the use of PRO-DENSE in the reconstruction of cavitary bone defects. In contrast to PMMA, PRO-DENSE reconstruction ultimately leads to remodeled native bone that may circumvent early joint degeneration thought to result from the altered load-bearing biomechanics of bone cement.\textsuperscript{4,18} Likewise, the use of PRO-DENSE eliminates the risks of disease transmission, deep infection, and nonunion associated with allograft and obviates the possibility of donor-site morbidity and limited supply associated with autograft.\textsuperscript{5,7,9} Although the current technique provides early structural support, it minimizes the possibility of early collapse or fracture.\textsuperscript{3} Complete radiographic resorption and new bone incorporation is typically seen by 5 months postoperatively with PRO-DENSE.\textsuperscript{13} In comparison, the incorporation of microparticulate allograft bone may take more than 1 year.\textsuperscript{8} Finally, due to the manufactured nature of synthetic products, particle size and consistency are predictable.

Unfamiliarity with the typical radiographic appearance of PRO-DENSE reconstructions and associated difficulty in detecting local recurrence may be a disadvantage of this technique. Following PMMA reconstruction, tumor recurrence is easily recognized as an expanding lucency adjacent to the cement; however, surgeons and radiologists may have difficulty interpreting the changing appearance of PRO-DENSE reconstructions over time.\textsuperscript{9,19} The current authors’ previous study established a preliminary description of these appearances, which are becoming more familiar to radiologists and orthopaedic surgeons.\textsuperscript{13}

Among the current 24 patients, patients 3 and 19 sustained local tumor recurrences. Patient 3 had a proximal humeral giant cell tumor of bone, and patient 19 had a distal radial aneurysmal bone cyst. These patients had relatively large tumors in areas with little surrounding bone stock. Although they underwent extended intralesional curettage, including high-speed burring to further debride their cavitary defects, the anatomical locations of these tumors mandated less aggressive resections than for other patients in the study. This may have contributed to their recurrences.

Similar to other foreign materials, infection in the setting of PRO-DENSE may require removal of all grafts for complete eradication. One deep infection occurred in the current study in patient 17 secondary to a superficial wound breakdown. He was successfully treated with complete PRO-DENSE removal, extensive irrigation and debridement, implantation of antibiotic-laden PMMA, and a 6-week course of intravenous antibiotics. In a series of 15 patients treated with calcium sulfate reported by Kelly and Wilkins\textsuperscript{20} and a series of 56 patients treated with PRO-DENSE reported by Fillingham et al,\textsuperscript{21} 1 case of infection in each study was successfully treated with irrigation and debridement without complete graft removal or antibiotic-laden PMMA.

Most patients in the current series required a smaller amount of PRO-DENSE than their preoperative radiographic tumor volume. The mean volume of injected PRO-DENSE was 15.6 cm\textsuperscript{3} compared with a mean preoperative radiographic tumor volume of 41.0 cm\textsuperscript{3}. Benign bone tumors often slowly expand their host bones as they grow, which leads to increased radiographic tumor volume.\textsuperscript{22}

The economic effect of reconstruction with PRO-DENSE is unclear. To the current authors’ knowledge, no cost analysis of synthetic bone substitutes used in
oncologic surgery has been performed. Significant cost is associated with allograft harvest, screening, and storage.\textsuperscript{23} In spinal fusion surgery, the 2-year total costs associated with autograft bone or a synthetic bone graft substitute were comparable, but the autograft group required greater expenses due to additional complications, and treatments and revision procedures.\textsuperscript{24} Comparable economic data and descriptions of PRO-DENSE in any setting are lacking, and costs may vary between health care systems.\textsuperscript{10} Further study is necessary to estimate the immediate and long-term economic effect of the current technique.

To the authors’ knowledge, 1 other report has examined the use of a CaSO\textsubscript{4}/CaPO\textsubscript{4} synthetic bone graft composite in the surgical management of primary bone tumors. Fillingham et al\textsuperscript{21} reported 56 patients treated with PRO-DENSE after management of a variety of benign bone lesions. Most patients returned to normal function with high Musculoskeletal Tumor Society functional outcome scores at a mean follow-up of 42 months. Three patients sustained local recurrences, 1 sustained a superficial infection treated with oral antibiotics, 1 sustained a deep infection requiring irrigation and debridement, and 2 sustained postoperative fractures. Thirteen patients with unicameral bone cysts were treated percutaneously. The study did not report the timing or achievement of early functional recovery.\textsuperscript{21}

Few studies have reported bone defect reconstruction after intralesional curettage of benign bone tumors with other synthetic bone substitutes. Calcium sulfate alone, β-TCP alone, and CaSO\textsubscript{4} combined with hydroxyapatite were associated with high Musculoskeletal Tumor Society scores in retrospective series.\textsuperscript{20,25-27} In these reports, infections, fractures, and local recurrence occurred in up to 7%, 8%, and 15% of patients, respectively, but early functional recovery was not reported. Saikia et al\textsuperscript{28} reviewed 25 patients who underwent reconstruction with β-TCP or hydroxyapatite and reported a mean time to full weight bearing of 14 weeks. Almost one-third of the reconstructions in this series included autograft or hardware with the bone substitute. Siegal et al\textsuperscript{29} reviewed 51 patients who were followed for a mean of 18 months whose bone defects were treated with a composite of β-TCP and autogenous bone marrow aspirate. Forty-seven patients progressed to unrestricted activities of daily living at 6 weeks, and an unspecified number of patients were also treated with internal fixation, hinged bracing, or casting.

The current study was limited by its retrospective cohort design. No control or comparative data were used, and data collection was subjected to recall and misclassification bias. The database did not include functional outcome scores or objective range of motion data, which increases the possibility of poor clinical outcomes despite early weight bearing. Many patients were followed for less than 2 years, which limited the assessment of oncologic outcomes.

However, the authors described a relatively large cohort of patients with near-complete data, and the majority of patients were followed for more than 1 year. All patients were followed for at least 6 months, except for 2 patients who were lost to follow-up. A strength of this study is the relative novelty of PRO-DENSE use in bone tumor reconstruction; this study is the first to examine the early return to functional activities of daily living associated with its use. Confounding factors that may affect timing to functional recovery but were not controlled for in this study include varying proximities of the tumors to articular surfaces, varying involvement of subchondral bone, and varying use of short-term postoperative bracing.

**Conclusion**

PRO-DENSE was a viable option for the reconstruction of cavitary bone defects following intralesional curettage of primary benign bone tumors. The use of the CaSO\textsubscript{4}/CaPO\textsubscript{4} synthetic bone graft composite PRO-DENSE was associated with rapid biological integration and early functional return to activities of daily living with no complications related to the use of the synthetic bone graft. Future studies should prospectively compare oncologic and functional outcomes relative to other reconstructive techniques and evaluate the associated economic effect.

**References**


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