Erik M. Erbe
Ted D. Clineff
Gina Gualtieri

Comparison of a new bisphenol-a-glycidyl dimethacrylate-based cortical bone void filler with polymethyl methacrylate

Received: 18 December 2000
Accepted: 12 March 2001
Published online: 24 August 2001
© Springer-Verlag 2001

Abstract A newly formulated and reinforced bisphenol-a-glycidyl dimethacrylate (bis-GMA) resin (Cortoss/Orthovita, Malvern, Pa.) was compared with Simplex P polymethyl methacrylate (Stryker Howmedica Osteonics, East Rutherford, N.J.) in rabbits for up to 52 weeks and in sheep for up to 78 weeks. As seen in scanning electron microscopy and histology examinations, both implant materials were surrounded by bone at late time periods, with fibrous layers of connective tissue seen in half the Simplex P specimens. No clinically significant safety differences between implant materials were apparent. Interfacial bond strengths between the implant and bone generally increased with time, but were 4.5-fold greater with Cortoss than Simplex P at 24 weeks, and 100-fold greater at 52 weeks. Forces required to displace 316SS rods held in place

with Cortoss were consistently greater than forces to displace rods held in place with Simplex P. No statistically significant differences in displacement forces were found between rods held in place with Cortoss polymerized in situ and rods held with prepolymerized Cortoss. Interfacial bond strengths were greater for Simplex P that was polymerized in situ than for prepolymerized polymethyl methacrylate specimens. Cortoss synthetic cortical bone void filler is a good candidate material to fix implants in bone. It has characteristics consistent with long-term safety and has a better ability to bond to bone than Simplex P.

Keywords Bone cement · Bone substitute · Bone regeneration · Polymethyl methacrylate · Bisphenol-a-glycidyl dimethacrylate

E.M. Erbe (✉) · T.D. Clineff · G. Gualtieri
1247 Berwyn-Paoli RD, Berwyn,
PA 19312, USA
e-mail: emerbe@aol.com,
Tel.: +1-610-2510971

Introduction

Bisphenol-a-glycidyl dimethacrylate (bis-GMA) resins have been studied in orthopedic applications since the late 1970s [21]. Various formulations were developed in efforts to reduce the amount of leachable unreacted monomer, to avoid high local temperatures during polymerization, to improve mechanical properties, and to enhance direct bone contact [4, 19]. Current formulations of bis-GMA resins have achieved these goals of improved mechanical, chemical, and biologic properties [14, 18]. One such formulation is Cortoss synthetic cortical bone void filler, a bio-

compatible, bone-bonding, terpolymer cortical bone substitute containing bisphenol-a-glycidyl dimethacrylate (bis-GMA), bisphenol-a-ethoxy dimethacrylate (bis-EMA), and triethylene glycol dimethacrylate (TEGDMA) resins reinforced with synthetic combeite glass-ceramic particles to stimulate bone apposition at the interface, barium borosilicate glass for radiopacity and strength, and silica for improved viscosity.

For more than 20 years, polymethyl methacrylate (PMMA) bone cement has been used to reconstruct vertebral bodies that have collapsed as a result of trauma or tumor invasion [8, 9, 12]. Long-term studies report that these treatments are highly durable and that significant fail-

ures or secondary fractures related to cement are rare [1, 3, 6, 11, 13, 16, 17]. For at least the last 10 years, PMMA has been placed into vertebral bodies percutaneously using X-ray guidance to treat pain related to osteoporotic compression fractures or tumor invasion [5]. In a series of PVP surgeries extending to more than 300 patients, radiculopathies were found in only 1% of patients with fractures caused by osteoporosis [2]. Low complication rates, including infection, and high success rates for pain relief justify the use of conservative surgical approaches in the treatment of severely painful osteoporotic compression fractures.

Disadvantages of using PMMA cement in spinal procedures include the minimal working time and the radiolucency of the cement. Additional monomer is often added to the cement mixture to extend the working time. To improve radiopacity and visual control, additional contrast materials are blended into the mixture. Such changes in formulation reduce the mechanical properties of the cement [7, 10]. Cortoss synthetic cortical bone void filler has been developed in response to these deficiencies. It has been shown to be an optimal material with which to fix implants in bone, both with respect to its safety profile and to its greater ability to bond to bone in comparison with PMMA.

Cortoss is currently being evaluated clinically as a device to augment stripped-out bone screws. In addition, a multicenter study with more than 200 patients is planned to evaluate Cortoss as a bone void filler for percutaneous vertebral augmentation. The present study compares the biocompatibility and interfacial bond strengths of Cortoss synthetic cortical bone void filler with a commercially available PMMA bone cement implanted into rabbit femurs for up to 52 weeks and in sheep long bones for up to 78 weeks.

Materials and methods

Implant materials

Cortoss (Orthovita, Malvern, Pa.), which is formulated as a two-paste thermoset resin, was mixed in a static mix-tip upon simultaneous expulsion from a dual-chamber cartridge. Once expelled and mixed, the material hardens in approximately 5 min into an off-white composite with sufficient integrity to bear the load of body weight.

Simplex P (Stryker Howmedica Osteonics, East Rutherford, N.J.) is a commercial PMMA bone cement composed mainly of methyl methacrylate and methyl methacrylate-styrene (MMA-styrene). It is formulated with 10% barium sulfate for radiopacity. The manufacturer recommends that it be mixed under a vacuum and centrifuged to remove trapped air bubbles, and these recommendations were followed [20].

Surgery

Experiments with rabbits were performed in the animal facilities of Toxikon Corporation (Bedford, Mass.). Femoral defects (3 mm) were created bilaterally in the lateral cortex of the proximal condyles, the diaphyses, and the distal condyles of 25 New Zealand White

rabbits. Implant materials were injected into the defect sites using a 1-cc syringe. On the left side, the two proximal defects were filled with Cortoss and the distal defect was filled with Simplex P. On the right side, the proximal defect was filled with Simplex P and the two distal defects were filled with Cortoss. At 4, 8, 12, and 24 weeks, five animals were euthanized with injectable barbiturate.

Experiments with sheep were performed at the University of Pennsylvania Veterinary School of Medicine (New Bolton, Pa.). Four defects (4.8 mm in diameter×10 mm in depth) were created bilaterally in 22 sheep (1.5–2 years old). Defects in the distal radii were filled with either Cortoss or Simplex P. Defects in the greater tubercle of the proximal humeri were filled with 4.5×10-mm rods of Cortoss or Simplex P polymerized prior to surgery. Defects in the medial ulnae were fitted with 1×12-mm 316SS rods held in place with either Cortoss or Simplex P. Defects in the lateral calcanei were fitted with 316SS rods embedded in prepolymerized 4.5×11-mm dowels of Cortoss or Simplex P. Cortoss and Simplex P were randomized to the right or left side in each animal. Radiographs were taken at the midpoint of the study period and after euthanasia. After recovery from surgery, the sheep were allowed to graze. The sheep were killed at 6, 12, and 24 weeks (six sheep per time period), followed by two at 52 weeks, and two at 78 weeks [15].

Fig. 1A,B Histological images of rabbit specimens. **A** Cortoss implant with new bone in direct contact at 4 weeks. **B** Cortoss implant surrounded by bone at 24 weeks

Fig. 2A–I Rabbit histology.
A Cortoss implant at 4 weeks,
B polymethyl methacrylate (PMMA) implant at 4 weeks,
C Cortoss implant at 8 weeks,
D PMAA implant showing foci of necrosis at 8 weeks,
E Cortoss implant with new bone formation at 12 weeks,
F PMMA implant showing some bone formation at 12 weeks,
G Cortoss implant showing complete apposition of bone at 24 weeks,
H PMMA implant at 24 weeks,
I Cortoss implant with apposition of bone at 52 weeks

Fig. 3A–D Sheep histology. **A** Cortoss implant polymerized in situ with apposition of bone at 52 weeks, **B** prepolymerized Simplex P implant at 52 weeks, **C** Cortoss implant polymerized in situ in direct contact with bone at 78 weeks, **D** prepolymerized Simplex P implant surrounded by bone and connective tissue at 78 weeks

stron model number 8500, Canton, Mass.). Loads were measured using a 5-kN load cell.

Results

Scanning electron microscopy

In histologic images, Cortoss appeared to be in direct contact with new bone at 4 weeks in the rabbit, and was entirely surrounded at 24 weeks (Fig. 1).

Histology

Rabbit

At 4 weeks, periosteal and endosteal bone were seen at both Cortoss- and Simplex P-repaired sites, but a greater proportion of the bone margin appeared to be in contact with Cortoss than with Simplex P. Signs of mild inflammation and multinucleated cells were present to comparable extents for both types of implant at all time points (Fig. 2A,B) [15]. This is not uncommon.

Microscopic evaluation

Rabbit femora were examined by scanning electron microscopy and energy dispersive X-ray analyses, and, after further processing, by light microscopy. Histology sections were stained with hematoxylin and eosin (H&E) or Paragon. Selected rabbit sections were read in a blinded manner at the Hospital for Special Surgery (New York, NY), the NH Veterinary Diagnostic Lab (Durham, N.H.), and Pathology Associates International (Frederick, Md.).

Sheep sections were stained with either Paragon or H&E prior to histologic evaluation and digital image analysis. Selected sheep sections from the radii and humeri were read in a blinded manner at the NH Veterinary Diagnostic Lab.

Mechanical testing

Specimens from the ulnae and calcanei of the sheep were wrapped in saline-soaked towels and stored at -200°C until the time of pull-out testing [15]. Rods that were manually determined to be firmly in place were pulled from the defect sites at 1 mm/s for 2 mm (In-

At 8 weeks, peripheral resorption and vascularization were seen with progressing periosteal and endosteal bone formation within sites filled with either implant material. Foreign-body multinucleated giant cells, mild to moderate fibrosis, multinucleated giant cells, lymphocytes, and plasma cells remained to a similar extent in defects filled with either Cortoss or Simplex P (Fig. 2C,D).

New periosteal and endosteal bone was seen around both implant materials at 12 weeks. New bone was seen in areas where blood vessels had grown directly adjacent to Cortoss. Further vascular invasion of Simplex P was generally not seen (Fig. 2E,F).

The amount of bone was greater around Cortoss at 24 weeks than at 12 weeks. Some specimens of Simplex P were observed to lie adjacent to a layer of fibrous connective tissue; approximately half the specimens of Simplex P were adjacent to new bone (Fig. 2G,H). Cortoss appeared to have significant bone apposition by 52 weeks (Fig. 2I).

Sheep

Some endosteal bone formation and slight foreign-body reactions (fibrosis and macrophages) were seen in response to both implant materials at 6, 12, and 24 weeks, with no qualitative differences at early timepoints. At 52 weeks, both Cortoss and Simplex P were surrounded by endosteal bone and inflammatory cell infiltrates. Foreign-body multinucleated giant cells were seen around Cortoss, but were rarely seen around Simplex P at 52 weeks (Fig. 3A,B).

Microradiographic evaluation of sheep specimens

The extent of radiopacity around the perimeter of implants was significantly greater for Cortoss bone void filler polymerized in situ than for Simplex P implants polymerized in situ.

Displacement forces

Displacement forces generally increased with time (Fig. 4). Rods were more firmly held in place with Cortoss than with Simplex P at all time periods ($P \leq 0.01$). At 24 weeks, the force required to displace rods in prepolymerized Cortoss was 4.5 times as high as the force needed to displace rods in Simplex P ($P \leq 0.01$). Failure occurred at the bone/resin interface.

For rods fixed with bone void fillers that polymerized in situ, displacement forces for Cortoss generally exceeded those of Simplex P. However, the difficulty in normalizing the interfacial area due to varying interdigitation of Cortoss and PMMA made exact comparisons difficult.

For rods fixed with bone void fillers that were prepolymerized, displacement forces for Cortoss exceeded those of Simplex P at 52 and 78 weeks (Fig. 4).

Fig. 4 Displacement forces versus time. Rods were fixed in place in situ with either Cortoss or PMMA

For 316SS rods held in place with Cortoss, displacement forces did not depend upon whether the Cortoss was allowed to polymerize in situ or before surgery. There were no statistically significant differences between displacement forces of 316SS rods held in place with Cortoss that was polymerized in situ and those held in place by prepolymerized Cortoss.

Discussion

New periosteal and endosteal bone was formed within defect sites filled with either Cortoss or Simplex P, but the initial response was greater with Cortoss than with Simplex P. Subsequently, the periphery of Cortoss implants was invaded by new blood vessels that supported reparative osteogenesis; Simplex P was generally unreactive in terms of bone formation. Although both Cortoss and Simplex P were seen to be surrounded by bone in the long term (52 weeks in sheep, 24 weeks in rabbits), half the Simplex P specimens were separated from bone by a layer of fibrous connective tissue at 24 weeks.

Cortoss and Simplex P were different, however, in their abilities to bond to bone. Whereas the forces required to displace 316SS rods generally increased with time for both materials, displacement forces were greater for rods held in place with Cortoss than with Simplex P at every time point examined throughout this study, up to 78 weeks. At 24 weeks, the force required to break the bond between bone and Cortoss was 330 N versus 70 N for Simplex P, a relative strength difference of 4.5. The greater stability of the bone/Cortoss interface is attributed to a faster initial bone response and a greater degree of mineralization around Cortoss, as evidenced by digital analyses of radiographs.

Conclusions

Cortoss bone void filler has been shown to engender a biocompatible tissue response, resulting in significant ap-

position of new bone around the filler at 24 weeks in rabbits and at 52 weeks in sheep. Further, Cortoss increased the interfacial bone strengths between implants and bone by a factor of 4.5 after 24 weeks. Thus, it is concluded that this study presents supportive data concerning the safety and efficacy of Cortoss bone void filler, and that Cortoss is a promising candidate for clinical testing in ap-

plications requiring improved mechanical bone bonding between implants and host bone.

Acknowledgements The authors gratefully acknowledge Barb Dallap and Dean Richardson for their technical support of the sheep study.

References

1. Bini SA, Gill K, Johnston JO (1995) Giant cell tumor of bone. Curettage and cement reconstruction. *Clin Orthop* 245
2. Chiras J, Depriester C, Weill A, Sola-Martinez MT, Deramond H (1997) [Percutaneous vertebral surgery. Techniques and indications]. *J Neuroradiol* 24:45
3. Dreinhöfer KE, Rydholm A, Bauer HC, Kreicbergs A (1995) Giant-cell tumours with fracture at diagnosis. Curettage and acrylic cementing in ten cases. *J Bone Joint Surg Br* 77:189
4. Freeman MAR, Bradley GW, Revell PA (1982) Observations upon the interface between bone and polymethylmethacrylate cement. *J Bone Joint Surg Br* 64:489
5. Galibert P, Deramond H, Rosat P, Le Gars D (1987) [Preliminary note on the treatment of vertebral angioma by percutaneous acrylic vertebroplasty]. *Neurochirurgie* 33:166
6. Gitelis S, Mallin BA, Piasecki P, Turner F (1993) Intralesional excision compared with en bloc resection for giant-cell tumors of bone. *J Bone Joint Surg Am* 75:1648
7. Harper EJ (1998) Bioactive bone cements. *Proc Inst Mech Eng [H]* 212:113
8. Harrington KD (1981) The use of methylmethacrylate for vertebral-body replacement and anterior stabilization of pathological fracture-dislocations of the spine due to metastatic malignant disease. *J Bone Joint Surg Am* 63:36
9. Harrington KD (1986) Metastatic disease of the spine. *J Bone Joint Surg Am* 68:1110
10. Jasper LE, Deramond H, Mathis JM, Belkoff SM (1999) The effect of monomer-to-powder ratio on the material properties of cranioplastic. *Bone* 25:27S
11. Komiya S, Inoue A (1993) Cementation in the treatment of giant cell tumor of bone. *Arch Orthop Trauma Surg* 112:51
12. McAfee PC, Bohlman HH, Ducker T, Eismont FJ (1986) Failure of stabilization of the spine with methylmethacrylate: a retrospective analysis of twenty-four cases. *J Bone Joint Surg Am* 68:1145
13. O'Donnell RJ, Springfield DS, Motwani HK, Ready JE, Gebhardt MC, Mankin HJ (1994) Recurrence of giant-cell tumors of the long bones after curettage and packing with cement. *J Bone Joint Surg Am* 76:1827
14. Okada Y, Kawanabe K, Fujita H, Nishio K, Nakamura T (1999) Repair of segmental bone defects using bioactive bone cement: comparison with PMMA bone cement. *J Biomed Mater Res* 47:353
15. OrthoVita. Data on file. 1999.
16. Pals SD, Wilkins RM (1992) Giant cell tumor of bone treated by curettage, cementation, and bone grafting. *Orthopedics* 15:703
17. Persson BM, Ekelund L, Lovdahl R, Gunterberg B (1984) Favourable results of acrylic cementation for giant cell tumors. *Acta Orthop Scand* 55:209
18. Raveh J, Stich H, Schawwalder P, Ruchti C, Cottier H (1982) Biocement – a new material. Results of its experimental use for osseous repair of skull cap defects with lesions of the dura mater and liquorrhea, reconstruction of the anterior wall of the frontal sinuses and fixation of alloimplants. *Acta Otolaryngol (Stockh)* 94:371
19. Saha S, Pal S (1984) Mechanical properties of bone cement: a review. *J Biomed Mater Res* 18:435
20. Stryker Howmedica. The formula for success. Stryker® Howmedica website. <http://www.howmedica.com/simplex/pages/intro.html> (accessed August 24, 2000)
21. Vainio J (1978) Non-metallic fixatives in orthopedic surgery: some aspects of their present and future properties. *Arch Orthop Trauma Surg* 92:169