Osteointegration of a Bisphenol-a-Glycidyl-Dimethacrylate Composite and Its Use in Anterior Skull Base Defects: An Experimental Study in an Experimental Design Model of Cerebrospinal Fluid Leak

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Object: Promising clinical results were reported in watertight closure of anterior skull base defects (ASBDs) with bisphenol-a-glycidyl-dimethacrylate (bis-GMA)–based materials to prevent the cerebrospinal fluid leaks. However, interrelation of these materials with surrounding bones in histologic level, referred to as the osteointegration, has not been reported in the anterior skull base. In addition, an illustrative case with an ASBD that was repaired using a bis-GMA composite has been presented.

Methods: Twenty New Zealand rabbits were divided into 4 groups: control and sham groups consisted of 2 and 6 rabbits, respectively. The "skull base defect" group (n = 6) underwent a unifrontal craniectomy and an iatrogenic ASBD followed by creating a dural defect to obtain a cerebrospinal fluid leak. Similar bony and dural defects were acquired in the "repair with bis-GMA based allograft" group (n = 6), but the bony defect was closed with bis-GMA–based allograft.

Results: All animals in the "skull base defect" group died in 3 weeks after surgery. There were no animal losses in the "repair with bis-GMA based allograft" group at the sixth month. Histologic evaluation revealed complete osteointegration of bis-GMA composite with surrounding bones.

Conclusions: bis-GMA based allograft achieved a watertight repair of the ASBD. Histologic findings of this study showed that bis-GMA composite is a reliable material to be used in the closure of anterior skull base bony defects.

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Skull base bony defects provide a connection between the sterile intracranial compartment and contaminated spaces, such as the nasal cavity and paranasal sinuses. Moreover, these defects may be accompanied with dural tears, which may cause a cerebrospinal fluid leak (CSFL) that possibly leads to life-threatening complications, such as meningitis, pneumocephalus, or intracranial abscess.[1,2]

The CSFLs secondary to skull base fractures were reported to occur much more common at the anterior cranial fossa than at the middle and posterior fossae.[3] In addition, besides fractures, removal of bony structures during surgeries for anterior cranial fossa tumors may be a cause for CSFLs.[4] Therefore, preventing CSFLs due to anterior skull base defects (ASBDs) is one of the major problems that surgeons dealing with this region encounter in the clinical practice. However, the best method of achieving this is still debated.[5–10]

Helms and Geyer[11] emphasized the importance of the bony defect closure in addition to the dural repair to prevent CSFLs. They suggested using allografts that strongly hold to the surrounding bone, so that a watertight closure of the skull base bone defect may be achieved.[11] Results from one of our previous reports presenting cases with ASBDs that were successfully repaired using a bisphenol-a-glycidyl-dimethacrylate (bis-GMA)–based allograft, namely Cortoss (Orthovita, Malvern, PA), supported the importance of the bony defect closure.[10]

Bis-GMA composites were first used as synthetic bone void fillers in vertebral and long bone augmentation procedures and were found to be advantageous over other allografts in animal and clinical studies.[12–15] Their mechanical advantages, ease of application, and successful clinical results make them popular in operating theaters.[10,16]

Biomechanical characteristics of bis-GMA–based materials in the living tissue were evaluated in only 1 animal study, which was conducted in long bones of rabbits and sheep.[15] However, these materials have not been studied in flat bones forming the anterior skull base. In this article, by evaluating the osteointegration of a bis-GMA composite, we aim to test the effectiveness of this allograft in the closure of ASBDs that were created using an experimental traumatic nasoethmoidal CSFL model in rabbits. In addition, an illustrative case is presented. On the other hand, this study does not aim to compare the bis-GMA–based allograft to other materials available for the closure of ASBDs.

MATERIALS AND METHODS

This study was approved by the Institutional Committee for Animal Care and Use in Istanbul University Cerrahpasa Medical

Faculty, Istanbul, Turkey. Twenty adult New Zealand white rabbits were divided into 4 groups: control (n = 2), sham (n = 6), "skull base defect" (n = 6), and "repair with bis-GMA" (n = 6).

Animals were sedated via intraperitoneal injection of ketamine (50 mg/kg) and xylazine (10 mg/kg). Heart and respiration parameters were regularly checked during surgical procedures. Cefazolin (10 mg/kg) was given before and 6 hours after procedures via intramuscular injections.

No procedure was performed on the control group. The sham group underwent only a midsagittal skin incision, which was then primarily closed. The surgical procedure performed on animals was done as previously described.[17] In the "skull base defect" group, a midsagittal skin incision was made, and a unifrontal craniectomy was obtained. Then, a bony defect, connecting the intracranial cavity to the nasal cavity, was obtained with the help of a microdrill. Finally, a dural defect was formed to constitute a CSFL. In the "repair with bis-GMA based allograft" group, 6 animals initially underwent the same procedure as the "skull base defect" group. However, the bony defect was immediately closed with Cortoss. The dural defect was not repaired in both surgical groups.

Animals were checked in their cages on a daily basis for any local (incision) or general infection signs. At the end of the study, which was set to the sixth month after the procedure before the study, there was no loss of animals in control, sham, and "repair with bis-GMA based allograft" groups. On the other hand, all 6 animals in the "skull base defect" group died within 3 weeks after the surgical procedure.

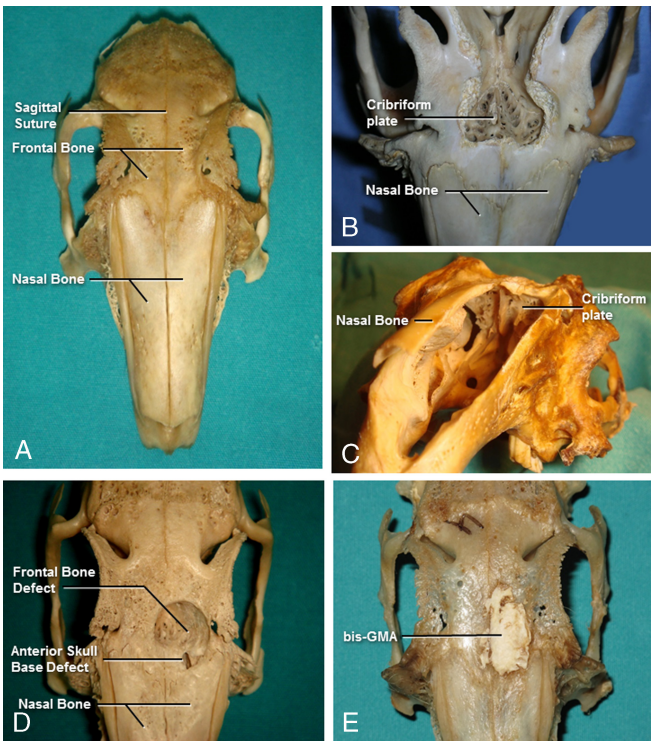

FIGURE 1. A, View from above. The rabbit skull after soft tissues have been removed. No surgery was performed on this specimen. B, View from above. The frontal bones have been removed to explore the cribriform plate at the anterior skull base. C, View in coronal plane. The left nasal bone has been removed to have a view of the nasal cavity and the cribriform plate. D, View from above. A unifrontal craniectomy and an ASBD were created in this specimen to obtain a CSFL. E, View from above. Bone defects have been repaired with bis-GMA–based allograft in this specimen. Macroscopic view reveals that the allograft was firmly holding to the bone and no gap was visible between the bone and the allograft.

All animals were decapitated at the end of sixth month. Their soft tissues were removed using a beetle box (Figs. 1A–C). Histologic microsections were obtained with the use of microtomes (Exakt Technologies Inc Cutting and Grinding Devices, Exakt Apparate bau GmbH & Co kg Norderstedt, Germany) at the Department of Oral and Maxillofacial Surgery, Cukurova University, Adana, Turkey.

RESULTS

After the removal of soft tissues, inspection of rabbit skulls with naked eye revealed that the skull base defects persist in animals in the "skull base defect" group (Fig. 1D). On the other hand, in the "repair with bis-GMA based allograft" group, we observed that the bis-GMA composite firmly attached to the surrounding bone without leaving any gap between the allograft and the bone (Fig. 1E). In addition, no signs of abrupt contours or irregularities were inspected. Rabbit skulls were also examined with computed tomography that verified gross inspection findings (Figs. 2A, B). Moreover, there was no leakage of the allograft into the nasal cavity (Fig. 2C).

Histologic examinations revealed that the entire circumference of the frontal craniectomy site and the skull base defect were in direct contact with the allograft proving a complete apposition and osteointegration. In addition, there was no fibrous encapsulation between bis-GMA–based composite and adjacent bone structures (Figs. 3A, B). Moreover, it seems that, in follow-up time, new bone tissue was formed toward the gaps of the bis-GMA composite (Figs. 3C, D).

Illustrative Clinical Case

This 35-year-old male patient admitted to our clinic because of recurrent meningitis and with a history of gunshot wound occurred 15 years ago. He underwent multiple operations in another neurosurgical unit for cranioplasty of the frontal bone with polymethylmethacrylate (PMMA) and the repair of the ASBD. After adequate antibiotic therapy for meningitis, he was taken to the operation room. The anterior skull base region was reached with a bicoronal incision and a bifrontal craniotomy. Some loose fibrotic tissues, thought to be ineffective to prevent the CSFL, were observed over the anterior skull base and were removed. A deep fissure such as bony defect, connecting the anterior skull base to the paranasal sinuses, was considered as not a geographical defect, so that a free flap was not considered as an option (Figs. 4A, B). Cortoss was plastered over the defect to close the openings (Figs. 4C, D). Postoperative period was uneventful, and radiologic work-up showed nothing abnormal (Figs. 4E–G). At the fifth year postoperatively, there is no sign of CSFLs or meningitis (Fig. 4H).

DISCUSSION

The best reconstruction method of the ASBDs remains to be a debated topic in the literature.[4,5,7–10] Moreover, possible involvement of a CSFL due to dural defects after an anterior skull base fracture or tumor invasion renders the decision making more complicated, because these defects, if inadequately treated, may develop serious complications, such as the pneumocephalus, meningitis, or intracranial abscess, which may cause mortality up to 10%.[3,18] Numerous methods proposing the use of autologous grafts or allografts have been reported in the literature to repair ASBDs and accompanying CSFLs. All these methods aim the same purpose: closing any dural defects and isolating sterile intracranial space from the contaminated nasal cavity.[10] On the other hand, there is no consensus on a chosen method yet.[3,4,8,9]

Some clinical series proposing the use pericranial flaps in the treatment of ASBDs previously indicated the necessity of obtaining a watertight seal of bony defects in addition to the dural repair.[3,4,8] However, a quick review of these series reveals continuing CSFLs

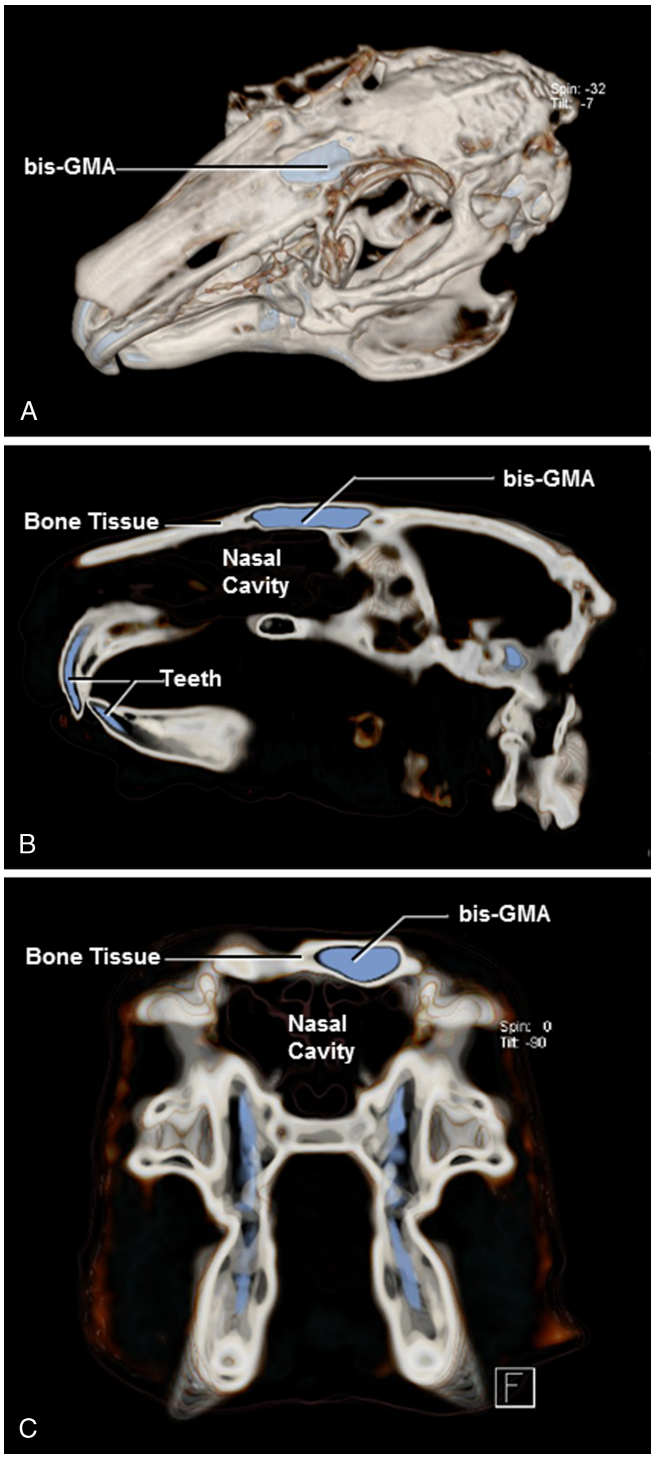

FIGURE 2. Three-dimensional reconstruction of computed tomography scans of rabbit skulls in the "repair with bis-GMA based allograft" group. Note that the allograft material and the enamel of teeth were presented with the same blue color, whereas the bone was presented with white color. A, Left frontolateral view. Fine borders between the bone and the bis-GMA composite can be seen. B, View in sagittal plane, at the level of repaired bone defect. New bone tissue formed around the bis-GMA composite. C, Similar to B, new bone surrounding bis-GMA composite holds the allograft in place. No leakage of the bis-GMA composite into the nasal cavity is present.

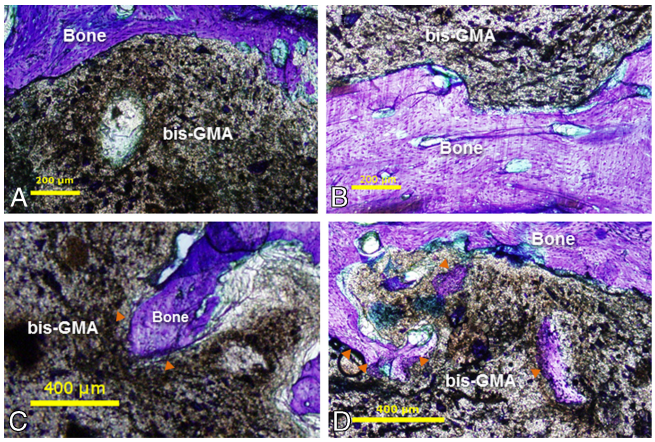

FIGURE 3. A and B, Histologic evaluation with toluidine blue staining at the end of the follow-up time revealed that the bis-GMA composite was in complete apposition to the bone without any fibrous encapsulation between 2 structures. C and D, Bone tissue advanced into the gaps of the bis-GMA–based allograft in the course of healing processes and ensured a complete osteointegration to the allograft.

after the surgery, which may be due to that suturing the soft tissue flaps to the bony skull base without any gaps may be practically hard to obtain.

On the other hand, to obtain a watertight closure of skull base defects, Helms and Geyer[11] proposed using allografts that show firm holding to the surrounding bone. This concept led us to use a bis-GMA–based allograft in the treatment of ASBDs. A previous report from our group presented successful clinical results in patients with ASBD, whose bony defects were repaired with commercially available bis-GMA composite (off-topic use), Cortoss.[10] No CSFLs or infections were observed in the follow-up period, and also, perfect cosmetic results were achieved in that series.

Cortoss is a nonresorbable bioactive composite and consists of bis-GMA resin reinforced with glass ceramic particles.[14] Its primary use was intended to be vertebroplasty, but it was found to be useful in other orthopedic procedures, such as the femoroplasty and the fixation of extremity fractures.[13,14,19] This expansion in clinical indications is probably due to studies showing advantages of bis-GMA composites over other materials, such as the PMMA that is the most widely used allograft in vertebroplasty.[14]

In this animal study, we showed for the first time the osteointegration of the bis-GMA–based material with flat bones forming the anterior skull base. The study was conducted with an experimental animal model that was proved to be a suitable method for evaluating CSFLs.[17] We believe rabbits are easier to handle than dogs or cats [17] and found that the anterior skull base anatomy of rabbits is eligible to study both CSFL and its repair. Note that these animals have wet noses under normal circumstances; thus, rhinorrhea should not be sought as a sign of CSFL. Instead, the rabbits were checked for signs of meningitis, such as aggressiveness, stagnancy, not feeding well, and/or changes in consciousness.

In our study, none of the animals treated with bis-GMA–based allograft had any complications, and no mortality was seen. On the other hand, animals without closure of the ASBDs died in short term after the surgical procedure. These data show that the allograft used in this study is a successful tool in preventing the CSFL and its possible complications. Besides these clinical data, we evaluated the specimens with histologic work-up and found that the bis-GMA composite showed a complete osteointegration with the bone tissue forming around the allograft. Moreover, there was no fibrous encapsulation separating the bone from the allograft material, which may be the reason behind the firm holding of the material to the bone.

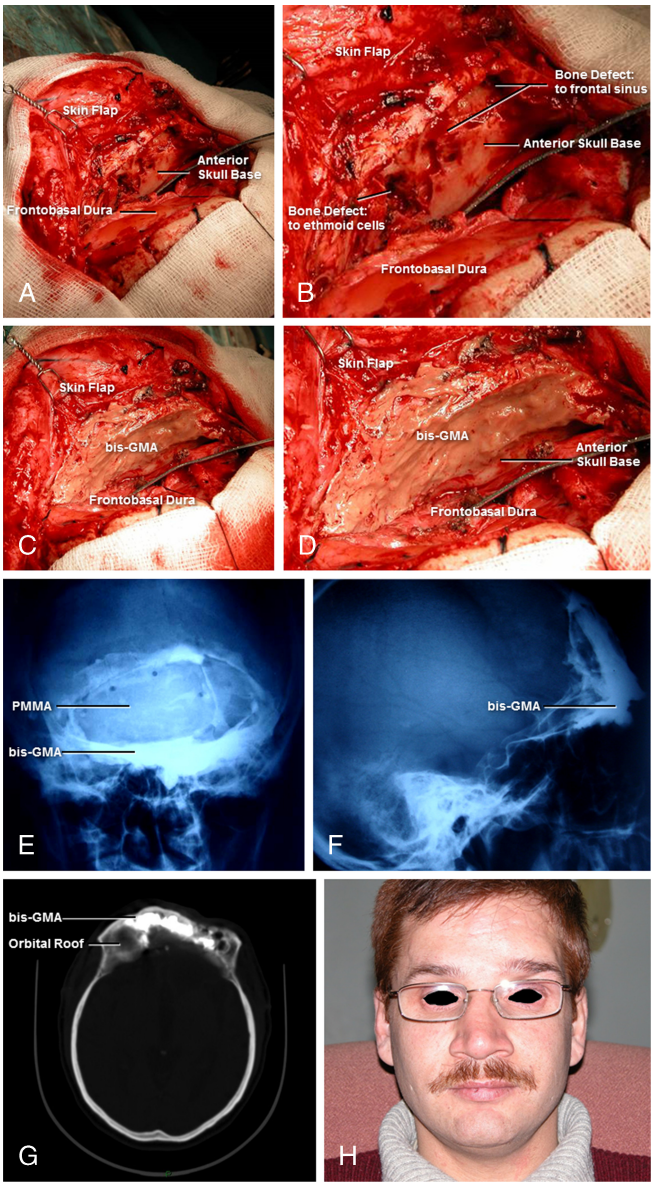

FIGURE 4. A, Intraoperative view of the presented case. A bifrontal craniectomy has been performed. B, Closer view of A showing that the bone defect at the anterior skull base was connecting the intracranial cavity to ethmoid cells and the frontal sinus. C, View of the operation site after the application of bis-GMA composite, which has a toothpaste-like form before setting. D, Closer view of C showing complete closure of openings to paranasal sinuses. Bis-GMA–based allograft borders posteriorly with the anterior skull base without any irregularities. E, Postoperative anteroposterior plain x-ray showing bis-GMA composite plastered over the anterior skull base. Note that this material shows strong density on x-ray, whereas the bone and the PMMA have similar radiolucency. F, Postoperative lateral plain x-ray showing the closure of the skull base defect. G, Postoperative computed tomography scan in bone window showing the reconstruction performed on the patient. H, Satisfactory results were achieved in the postoperative period in both surgical and cosmetic means.

Erbe et al[15] reported similar results in a previous animal study performed in long bones of rabbits and sheep. They concluded that bis-GMA–based material was holding to the bone much stronger than PMMA; 4.5 fold at 24 weeks and 100 fold at 52 weeks.[15] This finding is similar to what was reported in the study of Gheduzzi et al,[20] in which they compared the mechanical strength of bis-GMA–based material to the PMMA's and found that the bis-GMA–based material endured higher compressive and shear strengths. These results suggest that bis-GMA–based allograft is a good choice of material by means of weight-bearing ability. We did not compare the aforementioned mechanical characteristics of the bis-GMA–based allograft with other materials, because, unlike the vertebroplasty or orthopedic procedures, no toothpaste-like allograft material has been accepted as the gold standard in the practice of repairing skull base defects yet.

A widely used alloplastic material in the treatment of ASBDs is the hydroxyapatite bone cement. Although we have some limited experience with this material in our institution, we concluded that any liquid at the operative site before the setting time of this material, which is approximately 15 minutes,[9] has a great negative influence on postoperative stiffness of the material that jeopardizes the weight bearing.[10] Badie et al[5] mentioned that vascularized autologous grafts may also not show an adequate weight-bearing ability in long term. They offered application of a more rigid repair instead of "soft tissue alone" repairs in patients with longer expected survival, due to the postoperative development of meningo-encephaloceles.

On the other hand, Scholsem et al[3] emphasized the use of vascularized grafts and mentioned that they are superior to avascular free grafts, because vascularized grafts are more resistant to infections and easily fare with adjacent tissues in the healing process. Other clinical series using vascularized autologous grafts support this claim.[7,8,21–23] Although bis-GMA composites are nonvital materials, no infections related to this kind of allografts have been reported yet. Erbe et al[15] found that the periphery of bis-GMA composite was covered with new blood vessels, whereas half of the PMMA specimens were separated from the bone with fibrous tissue at the 24th week. The presence of these newly formed blood vessels may promote a vital and healthy bone tissue adjacent to the bis-GMA–based material and sustain low infection rates. Interestingly, Cortoss was found to be like a free radical scavenger, an important feature of this material.[24]

We have to underline that bis-GMA–based allograft may not be suitable in cases of very large bone defects. Glass ionomer cement proposed by Helms and Geyer[11] was stated to be available for shaping outside the body before application and hardening, thus allowing to obtain a material to fit exactly to a large bone defect. However, commercially available bis-GMA–based allograft, Cortoss, has a toothpaste-like consistency before application and has a setting time of around 5 minutes.[25] Application of Cortoss into very large defects may lead the material slipping into the nasal cavity. Therefore, we propose the use of Cortoss in rather not large defects or fissure such as fractures. In the presence of larger defects with too much loss of bone tissue, we prefer to use free rectus abdominis flaps as described.[23]

CONCLUSIONS

In addition to dural closure, watertight closure of bony defects is an essential step in the repair of ASBDs to prevent life-threatening complications. Numerous methods have been reported in the literature, but none of them is free from disadvantages. A bis-GMA composite has been used recently as synthetic bone void filler in cranial surgery without any complications. In the current study, we found that this clinical success is based on its mechanical characterization. Bis-GMA–based allograft material showed a complete osteointegration with surrounding bones in the anterior skull base of rabbits. In addition, its weight-bearing ability, low infection rates, and ease of use make this allograft a favorable choice in the repair of ASBD.

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