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A large calvarial bone defect in a child: osteointegration of an implant

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Keywords: Pediatric, Cranioplasty, Fibre-reinforced composite, Bioactive glass
Abstract

**Background:** This is an original report describing the long-term follow-up outcome of a cranioplasty. A large calvarial bone defect of a child was reconstructed with a bioactive and biostable non-metallic implant.

**Case Description:** This is a case study of a young child with an infantile fibrosarcoma of occipital bone. The malignancy in an occipital bone was removed from a child of 2.5 years of age, and the defect site was reconstructed with an on-lay glass fibre-reinforced composite – bioactive glass implant. After 5 years and 7 months, the follow-up examination showed no signs of a recidive. During the follow-up period, the contour of the reconstructed area followed skull anatomical development. Computed tomography demonstrated considerably large areas (approximately 70% of the total area) of bone on-growth to the peridural surface of the implant.

**Conclusions:** In the future, a synthetic cranioplasty material that is capable to integrate with cranial bone may be considered superior to cryopreserved bone grafts in younger age groups.
INTRODUCTION
Large cranial bone defect reconstruction methods in children are advancing. A cranial bone defect is a result of the treatment of traumatic brain injury, infection, a congenital anomaly, or a tumor. The purpose of cranioplasty, a neurosurgical reconstruction of a cranial bone defect, includes the restoration of the physical protection of the underlying brain, addressing a physiologic cerebral perfusion and pressure condition, to alter the skull’s cosmetic appearance, to improve one’s quality of life, and to prevent neurological symptoms caused by a missing bone flap.\textsuperscript{1,2} It has also been reported that the reconstruction of large cranial bone defects restores cognitive and functional impairments thus facilitating rehabilitation.\textsuperscript{3,4}

During craniectomy, the bone flap, if not fragmented or contaminated with infection, is saved for future use. The cryopreserved autogenous bone flap is the primary material for cranioplasty. The advantages include biocompatibility, osteoconductivity, its readily availability, and low cost. The main disadvantage is bone resorption, especially in younger age groups.\textsuperscript{5,6} Other strategies of cranioplasty currently in use include using a fresh autograft that is derived from split or full thickness calvarium, rib or crista iliaca; particulate calvarial bone graft; or an array of synthetic materials and self-resorbing materials.\textsuperscript{7}

A glass fibre-reinforced composite – bioactive glass (FRC – BG) implant was developed following a biomimetic approach to mimic the properties and structure of cranial bone.\textsuperscript{8} The advantages of a FRC – BG implant include a tough, light-weight, porous structure, which allows extracellular liquid perfusion and bone ingrowth with the osteoinductive and bacteriostatic properties by bioactive glass. These properties promote new bone formation.\textsuperscript{9} We have earlier reported about FRC – BG implant safety and biocompatibility in adults and pediatric population.\textsuperscript{10-12} We reported that, in a prospective follow-up study of 12 adult FRC – BG cranioplasties, the clinical outcomes were positive\textsuperscript{10}. One of the patients needed revision surgery. Second, we reported the follow-up results of a cohort of 8 pediatric patients.\textsuperscript{11} Three of these young patients needed revision surgery. Third, we compared the outcome of cranioplasty among different biomaterials including
autologous cryopreserved bone, FRC – BG, hydroxyapatite, and other synthetic materials. In this retrospective study, we included 84 consecutive patients, who underwent altogether 100 cranioplasty procedures for cranial bone defects during a ten-year period in our tertiary-level hospital. The overall complication rate was 32%, and revision surgery rate was 19%. After performing statistical analysis, there were no significant differences found among the four analyzed groups of implant materials. Finally, we reported a case study of a FRC – BG implant that was removed due to a late infection after functioning for 2 years and 3 months. The mechanical integrity was found to be intact. Fibrous tissue containing vascular structures, osteoblasts, collagenous fibers with osteoid formation, and clusters of hard tissue were observed near to the margin of the implant. Based on these positive clinical, histological, and mechanical findings, FRC – BG implants may be considered a feasible biomaterial for cranioplasty.

Here, we present a 2.5-year-old patient with a malignant occipital bone tumor removed with their bone defect reconstructed with a FRC – BG implant. The patient history, clinical findings, and imaging results after 6 years of follow-up are illustrated in detail.

MATERIALS AND METHODS
This is a case report study from a cohort including patients, who were recruited in prospective clinical trials studying glass fiber-reinforced – bioactive glass composite (FRC –BG) implants (ClinicalTrials.gov identifiers NCT01874613 and NCT-01202838). Both of the study protocols of these studies were reviewed and approved by the Joint Commission on Ethics of Hospital District of Southwest Finland (Protocol no. 167;125/2008 and Protocol no. 167;118/2012). All of the patients and/or their parents provided their informed consent. The aims of the studies were to investigate functional and aesthetic outcome and safety of cranioplasty using FRC-BG implants. The study was approved by Turku University Hospital, Turku, Finland. FRC – BG implants are currently in routine clinical use in Finland and Northern Europe.
This patient was selected for a case report, as she is the youngest child in the cohort and the only patient that has such a long-term follow-up.

**CASE DESCRIPTION**

The female patient was born with a 4-centimeter soft tissue tumor located at the occipital region. The tumor was excised, when the patient was 5 days old. Histologically the tumor was classified as infantile fibrosarcoma. The patient received oncological treatment. However, a recurrence of the tumor was observed 2 years and 6 months later. A local excision was repeated. The tumor was observed to infiltrate the occipital bone, and the histology was similar to the primary malignant tumor. The preoperative three-dimensional computed tomography scan revealed that a large area (144 cm$^2$) of occipital bone, including adequate margins, needed to be removed in one piece. We considered that the skull bone defect could not be left uncovered, and that conventional commercial implants of titanium or PEEK would not be suitable for this young patient. We decided to prepare a FRC – BG implant, which was manufactured at the Turku Clinical Biomaterial Centre (TCBC, Turku, Finland). The implant structure, materials, and polymerization process have been reported in detail previously. In brief, the implant was a sandwich structure consisting of outer and inner surface glass fiber laminates with a polymer matrix of dimethacrylates. The outer surface of the implant was a dense FRC laminate, whereas the inner surface was a mesh-like laminate with mesh hole size of 0.4 millimeter in diameter. The space between the outer and inner laminates was filled with particles of bioactive silicate glass (S53P4, BonAlive Biomaterials, Turku, Finland) of a particle size of 0.5 millimeter. FRC laminates were biostable, and the bioactive glass dissolved over time *in vivo*. The implant was designed as an on-lay implant with an on-lay margin width of 10 millimeters and a thickness of 0.8 millimeter. The margin was perforated for fixation screws. The weight of the implant was 22 grams of which the bioactive glass loading was 26.8 weight-percent. The implant was sterilized by the hydrogen peroxide plasma method (Sterrad, Johnsson and Johnsson, Irvine, CA).
After the surgical removal of the occipital bone, the reconstruction of the bone defect was performed with a preoperatively manufactured patient-specific FRC – BG implant. The implant that fitted exactly into the defect was anchored to the bone with four titanium screws. The child recovered uneventfully. The removed bone and also the soft tissue sample taken during surgery revealed the same malignant tumor. A large resection of the soft tissue and skin was performed two months later. During this surgery, the occipital skin and soft tissue were largely removed. The implant was covered with large full-thickness cranial skin flaps, and the areas from where the flaps originated were covered with free skin grafts. Recovery was uneventful. Normal cranial growth and normal cranial shape have been observed (Figure 1). No signs of implant loosening could be detected. Three-dimensional computed tomography revealed the exact positioning of the implant (Figure 2) and also large areas of peridural ossification on the inner surface and on the margins of the implant (Figure 3 and Figure 4). Intracranial bone coverage on the implant was 69% of the original defect (image analysis software CTAN: 2D/3D Image Analysis, Bruker, Kontich, Belgium). No signs of a tumor recidive were found during a six-year follow-up (Figure 5).

DISCUSSION

A skull bone reconstruction of a young patient was successful, and her cranial growth continues normally. The key features regarding the interaction among bioactive glass and bone, surgical operation, and the short-term and long-term clinical treatment are discussed.

A current trend in regenerative medicine shows the osteointegration of the cranioplasty material. Autologous bone and synthetic biomaterial may have osteoconductive and even osteoinductive properties. However, in the case of an autologous bone flap after 4-6 months of cryopreservation, an unsatisfactory treatment outcome is commonly seen. It has been demonstrated that cryopreserved skull bone flaps beyond four months do not show viable osteoblasts. Therefore, osteoinductivity is an essential property. When utilizing bioactive glass S53P4 in the clinical setting, bone healing is induced by bioactive glass S53P4. The bone healing progresses
from activation of stem cell differentiation toward a fibrous tissue phase of bone formation, simultaneously by biomineralization of the implant surface, which promotes osteoconduction. Another trend in regenerative medicine is the utilization of stem cells with a tissue engineering approach. However, utilization of the stem cell approach in cranioplasties has been clinically unsatisfactory, and further preclinical investigation is needed.

Here, we described a patient with a cranial bone defect reconstructed with a FRC – BG implant that had a durable FRC structure. In this age group, a spontaneous ossification of a cranial defect is possible as long as the dura and pericranium are intact. However, the cranioplasty was needed to protect the brain during bone healing. In this case, a follow-up of 5 years and 7 months confirmed margin-to-margin peridural bridges of new bone, and 69% of the defect was covered with new bone. Computed tomography of the patient showed also signs of intra-implant ossification, which we have demonstrated by histological analysis in a previous study.

The cranial bone growth and development after birth is a combination of sutural growth, remodeling, and displacement movements of growing bones. The spontaneous healing of cranial bone is considered possible from infancy up to 2 years. This is thought to be related to the rapid phase of brain growth, which produces mechanical pressure leading to acceleration of osteoneogenesis. In fact, apposition of bone along the edges of the fontanelles and thin periosteum-lined sutures keeps cranial bones separated for many years. Although the majority of the growth in the cranial vault occurs at the sutures, there is a tendency for bone to be removed from the inner surface of the cranial vault, while at the same time, new bone is added on the exterior surface. This changes the contour of the skull. In this particular case, the reconstruction was made to follow the occipital contour at the age of 2.5 years. By the follow-up period of 6 years, the contour of the implant matched well to the overall contour of the skull.
A FRC – BG implant provides a scaffold for bone regeneration. New bone is formed inside of the implant, where the bioactive glass is present and on the peridural surface of the implant. This case supports the implant’s functional mechanism being that bioactive glass S53P4 dissolves from the implant and releases ions, especially phosphate ions, which promotes mesenchymal stem cells of calvarial bones to differentiate into bone forming cell lines, and calcium ions, which biomineralize the FRC surface by calcium-phosphate minerals to make the implant surface osteoconductive. Ion release and ion exchange of bioactive glass S53P4 and extracellular liquid increases pH, which provides bacteriostatic properties.

Important observations found during the bone healing and osteogenesis on the surface of the implant were that new bone was found only on the inner surface of the implant. This suggests osteopromoting effects by the dura mater, which can be chemical and physical in nature. The outer layer of the dura mater functions as a skull’s inner periosteum and promotes bone growth like the periosteum at the sutures. Pulsatile fluid flow by the dura mater may also have an impact on osteogenesis. The surface of the FRC – BG implant seemed to offer a suitable environment for osteogenesis, which even allowed anatomical structures of protuberantia occipitalis and crista occipitalis interior to be formed (Figure 3).

It has been recommended not to reconstruct a cranial bone defect before the age of 2 years. After neurosurgical treatment of an intracranial tumor, when a bone flap is not affected by the tumor, the autogenous fresh craniotomy bone flap is clearly the best option for reconstruction. When the bone defect is not covered during the same operation, but the cranioplasty is performed later, the outcome with either a cryopreserved autograft or synthetic material is equal or favors a synthetic option. The resorption of cryopreserved bone affects up to 50 % of patients, and 22-50 % need a reoperation. As the risk of bone resorption seems to be strongly related to younger age, it has been suggested to consider, after decompressive craniectomy procedures on young patients, using primary cranioplasties with a synthetic material.
Some doubts have been raised regarding the use of synthetic cranioplasty material in a pediatric population. In their retrospective analysis of 71 pediatric patients, Fu and colleagues addressed the issue of potential skull growth restriction by a rigid cranioplasty material compared to an autologous bone graft. Patients were aged between 1 and 19 years at the time of cranioplasty. During the follow-up, no signs of skull growth restriction were observed. They concluded that a synthetic cranioplasty was a safe option, when an autogenous bone flap is unavailable. This result is in accordance with our experience of using cranioplasties in a pediatric population. The observations in the current case shows that even large cranial bone defects in growing children with a synthetic, bioactive implant is possible without hampering the future growth of the cranium.

CONCLUSIONS

In conclusion, we found considerable peridural ossification of a glass fibre-reinforced composite – bioactive glass implant six years after an operation of a malignant cranial bone tumor and cranioplasty. The contour of the reconstructed area followed the anatomical development of the skull during the six-year follow-up period. In the future, a synthetic cranioplasty material that is capable to integrate with cranial bone may be considered superior to cryopreserved bone grafts in younger age groups.

Conflicts of interest

Author PV is a board member of the Skulle Implants Corporation, which produces FRC – BG implants. Authors PV, KA, WS are shareholders of the Skulle Implants Corp. JPP has received speaker’s fees from the Orion Corporation and the Finnish Medical Association. Author JMP does not have any conflicts of interest.

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References


Figure 1

A pre-operative three-dimensional computed tomography scan of a 2 years and 6 months old child.

Figure 2

A follow-up three-dimensional computed tomography scan of a patient 5 years and 7 months after cranioplasty with fibre-reinforced composite – bioactive glass implant. The implant fitted into the defect. The position has not altered, and the screw-fixation is intact.

Figure 3

Three-dimensional computed tomography scan of a patient 5 years and 7 months after cranioplasty. The inner surface of a fibre-reinforced composite – bioactive glass implant seemed to offer a suitable environment for osteoneogenesis, allowing formation of peridural bridges of new bone. The anatomical structures of protuberantia occipitalis interior and crista occipitalis interior are shown.

Figure 4

A follow-up computed tomography scan of a patient 5 years and 7 months after cranioplasty. A series of axial computed tomography shows the cross-sectional composition of the implant, a normal cranial shape and osteogenesis.

Figure 5

An axial T2-weighted turbo spin echo image of a patient 6 months after cranioplasty. The contour of skull bone and a fibre-reinforced composite – bioactive glass implant follows a normal anatomical shape. No signs of a tumor recidive have been found during a six-year follow-up.
We wish to draw the attention of the Editor to the following facts, which may be considered as potential conflicts of interest and to significant financial contributions to this work.

Author PV is a board member of the Skulle Implants Corporation, which produces FRC – BG implants. Authors PV, KA, WS are shareholders of the Skulle Implants Corp. JPP has received speaker's fees from the Orion Corporation and the Finnish Medical Association. Author JMP does not have any conflicts of interest.

We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us.

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On behalf of all authors,

Jaakko Piitulainen, M.D., Ph.D.

23 October, 2018
Turku, Finland
List of Abbreviations

FRC  fibre-reinforced composite
FRC – BG  fibre-reinforced composite – bioactive glass
PEEK  poly-ether-ether-ketone
S53P4  S53P4 bioactive glass
TCBC  Turku Clinical Biomaterial Centre