Repair of Cranial Bone Defects in Children Using Synthetic Hydroxyapatite Cranioplasty (CustomBone)

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BACKGROUND: **In pediatric cases, the use of autologous bone tissue to repair cranial bone defects is often impossible. The synthetic hydroxyapatite bone substitute (CustomBone) can be a good alternative, especially in case of a large bone defect that has to be repaired.**

METHODS: **This study focuses on a pediatric series of 30 children who underwent cranioplasty with a CustomBone implant. Patient age ranged from 8 months to 16 years, with a mean age of 7 years and 8 months. The most common indication for cranioplasty was posttraumatic decompressive craniectomy.**

RESULTS: **No complications were reported. Cosmetic results were satisfactory in every patient. Only 1 implant had to be changed after severe head trauma because of an epileptic seizure in the early postoperative period. In all patients, cerebral blood flow improved during the postoperative phase. Complete implant osteointegration is a long process because mean time to begin was 13 months (range, 3–22 months). Mean patient follow-up was 6.7 years. Successful prosthesis integration depends on the accuracy of the preoperative model. The minimum thickness of the implant (4 mm) represents a challenge in very young children, but we used it with success in this series. Moreover, high costs represent another limitation for its use.**

CONCLUSIONS: **The CustomBone implant meets all necessary conditions for good clinical outcome: excellent protective properties, restoration of normal intracranial physiology, satisfactory cosmetic results, good integration in the autologous bone, and good resistance in case of trauma.**

INTRODUCTION

Cranioplasty may be required in both adults and children for different etiologies. Preferred material for cranioplasty is autologous bone tissue.[1-3] Sometimes, for patients with large cranial bone defects, the use of autologous material is not possible because there is not enough bone to harvest, and there is a significant risk of complications, even in children.[4-6]

In these cases, the use of substitute materials is necessary to avoid complications, and several materials are currently available. Synthetic hydroxyapatite [$Ca_{10}(PO_4)_6(OH)_2$] can be used as a good substitute to favor the colonization of true human hydroxyapatite, the main component of human bones, in 3 dimensions. The structure of hydroxyapatite promotes osteoconduction and osteoinduction. The properties of the molecular and tridimensional structure do not trigger a foreign body reaction, which explains the lack of implant rejection and the low risk of infection.[7] Implants are composed of 80% macropores and 20% micropores.[8-10] Microporosity promotes water imbibition.

In this study, we report our experience with CustomBone implants (Fin-Ceramica Faenza S.p.A., Faenza, Italy and Codman Neuro Inc., DePuy Synthes Co. Bristol County, Massachusetts, USA) in the treatment of cranial defects in children.

MATERIALS AND METHODS

Between 2006 and 2017, we operated on 30 children for cranial bone defects. A retrospective analysis of clinical and radiologic data was performed.

Key words
- Bone defect
- Cranial implant
- Cranioplasty
- Pediatric neurosurgery
- Reconstructive surgery
- Synthetic hydroxyapatite

Abbreviations and Acronyms
3D: 3-Dimensional
CPP: Cerebral perfusion pressure
CSF: Cerebrospinal fluid
CT: Computed tomography

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Patient age ranged from 8 months to 16 years with a mean age of 7 years and 8 months; 7 children were <5 years of age. There were 13 girls and 17 boys. Indications for cranial bone repair were as follows: in 5 cases after a tumor-invaded bone flap that was discarded for oncologic purpose, in 4 cases after infectious complications resulting from brain surgery (tumor or vascular surgery) with osteitis of the bone flap, and in the other 21 cases it was to repair a decompressive craniectomy. Demographic data are presented in Table 1. Details of these patients are subsequently described: 7 patients were operated on in other medical centers or abroad and the cranial flap was not preserved, in 2 patients they were very young at the time of the trauma and the cranial flap did not fit anymore in size when the cranioplasty procedure was done, in 5 patients the bone flap was discarded at the time of the procedure which was done in case of intracranial hypertension because of an epidural and subdural empyema with bone osteitis, and in 7 patients their own reimplanted bone flap had lysed several months after and they therefore needed a bone plasty. Mean timing of the cranial repair, excluding cases related to infectious pathologies was 3.4 months (minimum, 1 month; maximum, 6 months). Mean timing of the cranial repair secondary to infection was 13 months (minimum, 12 months; maximum, 15 months).

All patients were followed-up except one who moved to another European country. Length of follow-up ranged from only 1 year to 11 years, with a mean follow-up of 6.7 years. Bone defect locations are summarized in Table 1.

Cerebral blood flow was monitored in all patients before cranioplasty and controlled 6–12 months after cranioplasty.

All patients benefited from clinical follow-up and had at least 1 head computed tomography (CT) scan to check for bone neoregeneration, to check for implant osteointegration, and to make sure there was no prosthesis dislocation. In accordance with our protocol, the first CT scan was usually performed 48 hours after surgery, followed by other scans at 3 months, 1 year, and then once every 2 years. We did not use a scale to assess the extent of prosthesis osteointegration, and we simply monitored bone tissue regeneration. The CT scan also allowed us to monitor implant alignment with surrounding bones, especially with the use of 3-dimensional (3D) reconstruction.

Aesthetic results were either deemed satisfactory or unsatisfactory by the family, the patient (when possible), and the medical team.

RESULTS

The cranial implant was inserted in each patient without difficulties. Results were deemed satisfactory in all but 2 patients, with a defect in the fronto-orbital region in one case and a protruding vertex in the other. In the latter case, the implant was well attached but there was a palpable protrusion of the vertex with barely any aesthetic impact. In the case with the fronto-orbital implant, symmetry was not perfect but better than before surgery: it was a case of a severe fronto-orbital deformation resulting from an extended surgery for an exophytic optic glioma that needed the removal of the optic nerve in a young child.

Only 1 patient had complications in the form of a pseudomeningocele, which required drainage with a pseudomeningocele-peritoneal shunt without valve over 6 months.

Table 1. Demographic Data of Our Series

Variable	Number of Patients (%)
Sex	
Male	17 (56.7)
Female	13 (43.3)
Localization of the CustomBone	
Right hemisphere	12 (40)
Left hemisphere	8 (26.7)
Frontotemporal	4 (13.3)
Bifrontal	5 (16.7)
Posterior fossa	1 (3.3)
Indication for cranial repair	
Tumor invaded bone	5 (16.7)
Infections	4 (13.3)
Decompressive craniectomy	21 (70)

This was the only case where the implant broke after accidental cranial trauma for a fall consecutive to a seizure related to post-traumatic epilepsy. The patient's epilepsy, a consequence of her neuropsychologic impairment, resulted in frequent falls and head injuries. A new surgery was required to replace the damaged implant and the meningocele-peritoneal shunt, which was obstructed by implant debris. In this particular case, we used the copy of the implant that was available in case of surgical accident in the operative room, and we did not have to wait for a new one to be manufactured.

The occurrence of only 1 single accident is proof of the good resistance of the CustomBone implants. Therefore, we do not recommend the use of a protective helmet, even in patients with epilepsy, because the rate of complications is relatively limited and these patients are not at a more elevated risk of severe trauma.

In accordance with our protocol, all patients underwent CT scan 3 months and 1 year after cranioplasty. There were 2 exceptions: one patient moved back to his country of origin and another patient was lost of follow-up after 6 months for unknown reasons.

Images obtained from the CT scans, particularly 3D CT scans, were used to look for the outline of the implant. In all cases, bone bridges could be observed, proof of the osteoconductive and osteoinductive properties of the implant; it also proves that newly formed bone tissue can be easily absorbed into the porous structure of the implant (Figure 1). On average, early stages of osteointegration could be seen 13 months after initial cranioplasty (range, 3–24 months) (Figure 2).

In only 2 patients <2 years of age, a discrepancy between bone thickness and implant thickness could be noticed. The edge of the implant was 1 mm above surrounding bones, with no obvious functional or aesthetic impact and without sign of compression of the underlying brain.

Generally, implants were fixed using nonabsorbable suture materials (Figure 3), except in recent cases where metallic CranioFix (B Braun Aesculap, Tuttlingen, Germany) (Figure 4)

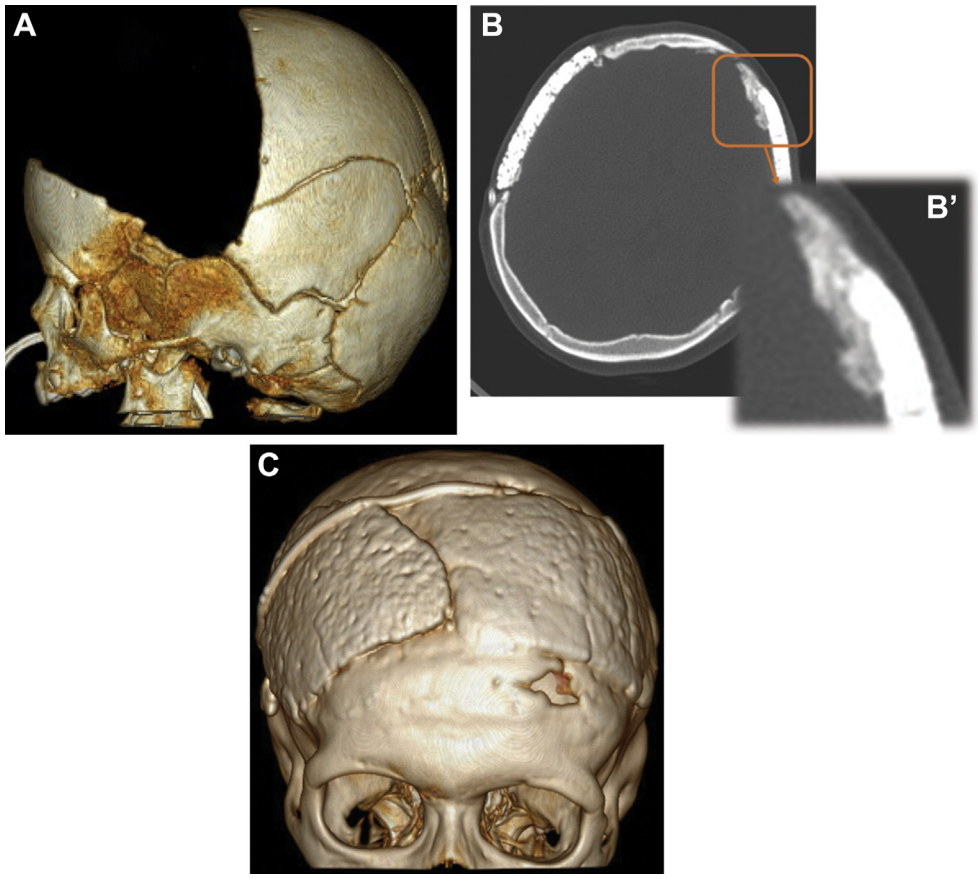

Figure 1. (**A**) Three-dimensional (3D) reconstruction of a computed tomography (CT) scan performed after a bifrontal bone flap. (**B**) A 3-year postoperative CT scan showing good integration of the bifrontal implant with some parts of complete osteointegration (**B'**). (**C**) 3D reconstruction of the 5-year postoperative CT scan showing several bone bridges between the implant and surrounding bone.

was also used without any alteration of the implant structure and, most importantly, without implant breakage. However, this fixation needs to be used with precaution to avoid breaking the implant.

Before cranioplasty, cerebral blood flow monitoring showed that total blood flow was reduced or blood flow was reduced in the frontoparietal or parieto-occipital regions. The reduced perfusion of the frontiers areas of the brain is always associated with clinical manifestations. In all cases, cerebral blood flow was normal when monitored 6–12 months after cranioplasty, which confirms that the CustomBone implant helps to restore a normal intracranial physiology (intracranial homeostasis) (Figure 5).

Long-term cosmetic results were deemed good to very good, with no complaints from families or older children (Figure 6), and no need for later aesthetic surgery.

DISCUSSION

Cranioplasty represents an old but rare surgical procedure, but it is a relatively common procedure in neurosurgery. The most common cause is posttraumatic decompressive craniectomy. Other causes include bone flap replacement after an infectious complication with osteitis or removal of a tumor-invaded bone flap, and ischemic complications.[11]

History of Materials Used for Cranioplasty

Several materials have been used to repair cranial bone defects: human cartilage, methyl methacrylate, vitallium, ticonium, tantalum, and titanium. All these materials have advantages and drawbacks,[4,5,12-14] and even today, there is no consensus about which one is the best. The first materials to be used in the modern era were cartilage and bone from the human body, but they both resulted in a high number of implant failures and infections.[4,5] Autologous bone grafts have been generally considered as the criterion standard of calvarian reconstruction. However, in some cases, the extension of the lesion does not allow its use. Therefore, it is necessary to find materials that can substitute the autologous bone that is generally recommended for the properties of molding and the capacity of integration of the growing pediatric skull.[15] Many materials have been used for cranioplasty: vitallium was highly resistant but not flexible enough for remodeling.[12,13] The

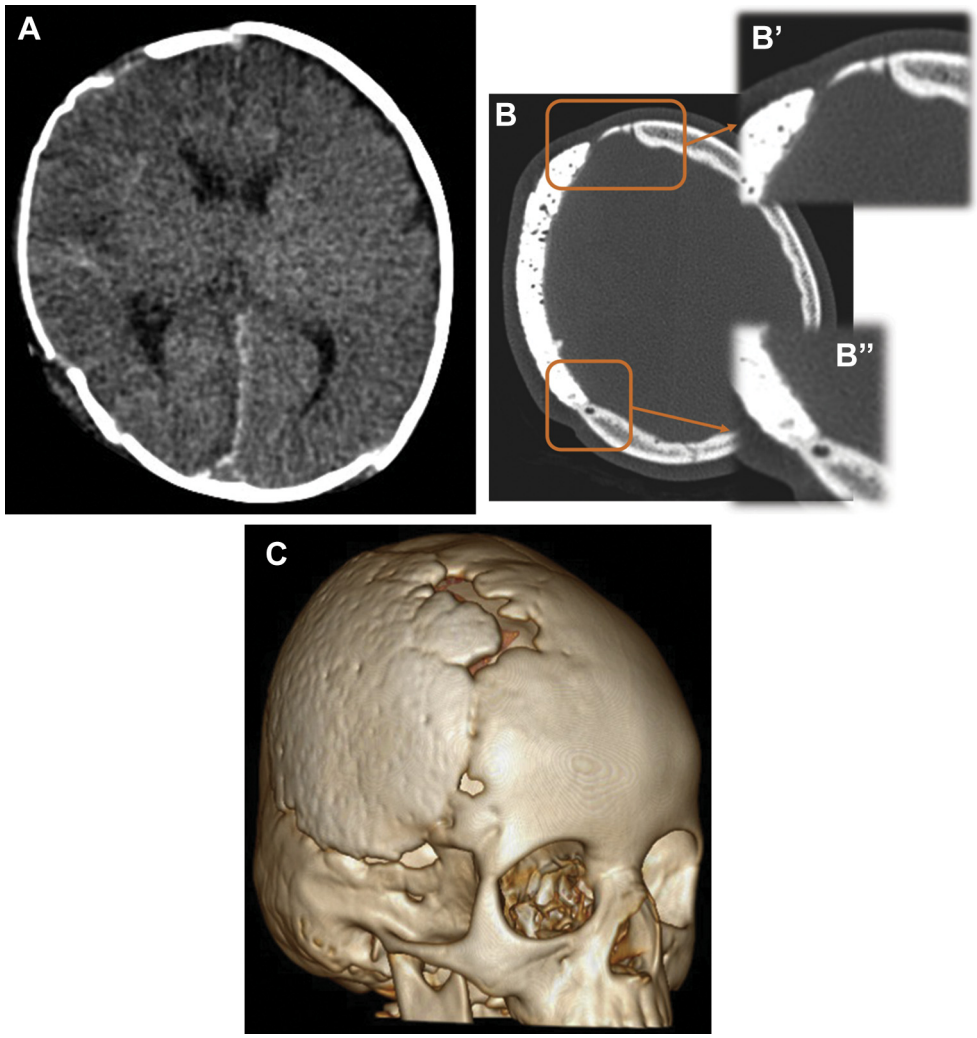

Figure 2. Case of the youngest patient who underwent decompressive craniectomy at the age of 8 months. (**A**) Postoperative computed tomography (CT) scan just after decompressive craniectomy. (**B**) A 6-year postoperative CT scan showing good integration of the implant with some bone bridges between the implant and the cranium without complete osteointegration of the implant (**B'**) and some completely osteointegrated parts of the implant (**B"**). (**C**) Three-dimensional reconstruction of the CT scan showing several bone bridges between the implant and surrounding bone.

biocompatibility of ticonium and tantalum was good, but there were several issues with these materials: they were expensive, they were associated with headaches, and above all, they were associated with thermal conduction problems that affected the underlying nervous system with possibility of damage.[14] As for titanium, it certainly is hard to work with but it is also cheaper, has good biocompatibility, and magnetic resonance imaging scans can easily and safely be performed on patients with titanium implants without any risk of artifacts appearing on the images.[5] History shows that the ideal substitute for cranial repair should be resistant, biocompatible, adaptable, reasonably priced, and easy to use in reconstructive surgery to ensure a good aesthetic result.

Synthetic hydroxyapatite seems to fulfill requirements to be used as a material for cranioplasty.[9] As shown in pediatric pathology,[6] it is adaptable, aesthetic results are good, complications are rare, and it favors the autologous ossification process.

Why Repair a Cranial Bone Defect?

The cranium is normally closed, which allows to maintain the physiologic environment of the brain and the intracranial pressure.

When the cranium is opened, the brain is not in its natural physiologic condition; consequently, brain function is altered because cerebral perfusion pressure (CPP) and cerebral blood flow

Figure 3. Operative view: the implant is fixed with resorbable sutures.

are altered with a deficit in perfusion of the brain, or in some cases in the frontier zones with clinical manifestations.[16,17]

When the skull is open, intracranial pressure and atmospheric pressure equalize and the physiologic conditions in which the intracranial pressure is 1 atm plus 15 mm Hg are lost and everything is equalized to 1 atm. This condition results in motor disorders and higher brain function impairment, with an impact on memory, concentration, academic performance, and so forth. Chronic headaches can also appear, especially when the patient is standing up. Cerebrospinal fluid (CSF) circulation is consequently altered.[18] This clinical picture is similar to slit ventricle syndrome.[19] Generally, patients present with fatigue that obliges them to stay always at rest, especially during school time.

Finally, the brain is not naturally protected and injuries can have more severe consequences, mainly in cases of trauma with a sharp object that can penetrate an area of little resistance.[20]

Aesthetic results are important in reconstructive surgery because other people's glances can negatively affect patients' self-esteem, especially when the bone defect is located on the frontal region which altered the forehead shape.

In pediatric cases, it is often difficult to repair very large defects with autologous bone because the thickness of the bone usually does not permit splitting, especially in very young children. In older cases, if we consider repair using slit autologous bone, we need a very large approach with increased risk of hemorrhages or infections at the level of the donor site. For these reasons, we prefer to use alternative implants even in older patients.

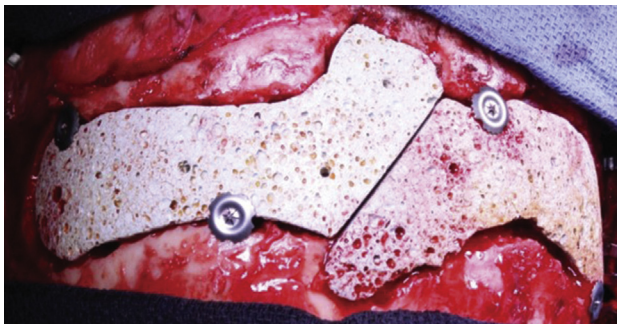

Figure 4. Operative view: the implant is fixed with CranioFix.

Successful osseointegration of the custom bone depends on the accuracy of the 3D model (**Figure 7**), which can be modified by the surgeon before the production of the definitive model. A CT scan with 2-mm cross sections, a resolution of at least 512 × 512 pixels, and a gantry rotation of 0° should be performed as requested by the manufacturer. The surgeon may perform a complementary bone resection so that the edges of the implant are perfectly aligned with surrounding bones; this gives better aesthetic results, especially when cranioplasty is performed in the frontal region.[11,21-24] Moreover, corrections can be made during surgery with a bone cutter or a drill without altering implant structure or creating weak points which could lead to implant fracture. Generally, the model has to be implanted not too long after its conception in young children because the physiologic growing process can modify the receiving area, making it difficult to use the implant to close the bone defect.

The implant can easily be fixed, either with nonabsorbable suture materials or with metallic CranioFix, like we did on a few occasions, but in the former cases, the surgeon has to be aware of the pressure closing the graft in order not to break it.

Our pediatric series has shown that patient age is not a limiting factor in itself. However, it is not advised to perform cranioplasty in patients <2 years of age[6] because prostheses cannot be <4 mm thin; otherwise, their inner structure would be altered and they would not be resistant enough. However, we have operated 7 children <5 years of age, and among those, 2 were <2 years of age. We are aware that a thinner prosthesis could be better adapted for the bone of newborns and infants. However, for now, the thickness of the CustomBone is not responsible for brain compression and it is possible to model the step between the plasty and the bone edge of the skull with a high-speed drill.

Other publications have demonstrated the efficiency of CustomBone implants and the lack of associated complications, infections, and prosthesis instability.[6,7,25]

Protective Properties of CustomBone Implants

Our experience shows that CustomBone implants do protect the patient's brain. All patients who were followed-up for >3 years had completely normal lives, without prosthesis-related adverse effects and a good quality of life.

The single occurrence of implant fracture, the consequence of severe and repeated head injuries, is further proof of the resistance of the implant and of its good capacity to protect the central nervous system. Generally, we do not recommend helmets for children because they are constraining and bothersome for them. Moreover, children with cranioplasty are not more at risk for head injury than children without cranioplasty, but in our experience, children with a helmet are limited in their daily life.

In our patients, after cranioplasty with a CustomBone implant, CPP went back to normal in the watershed areas and in the hypoperfused areas. This has already been reported in the scientific literature.[16,17] The measure of the CPP and CBF before and

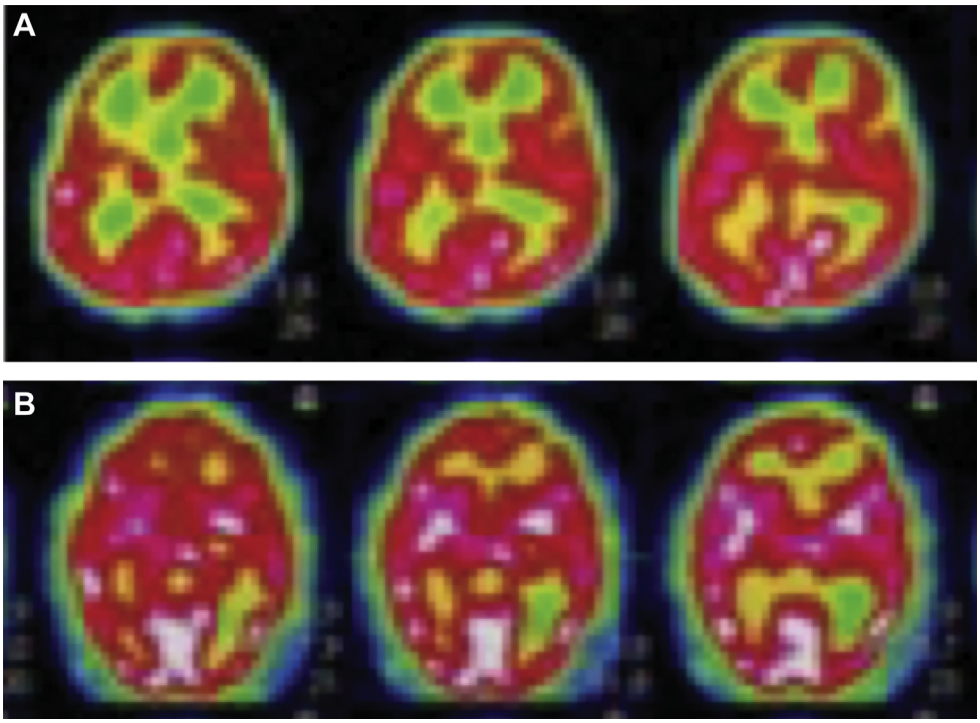

Figure 5. Postcraniectomy study of cerebral blood flow with hypoperfusion on the frontal region (**A**), which recovers after cranioplasty (**B**).

after implantation of the prothesis has shown that the process of closure of the skull is a real necessity to restore the physiologic condition for the brain. If the decreased cerebral flow is not well tolerated by the patient (headache and slow neurologic performance), it is possible to shorten the delay of the reconstruction because it helps to resolve the symptoms. We think that the 1 year delay for the cranial vault reconstruction after an infection should be respected even if the CPP and CBF are decreased. This concept is related to our general experience with bony infections that need 1 year to be completely sterile, and the hydroxyapatite material is not an exception.

It seems that this implant has excellent protective properties with osteogenic and osteoconductive properties of the CustomBone that favor a more physiologic reparative process. Moreover, normal intracranial physiology was restored thanks to the implant, as shown by clinical evolution of patients and improved blood flow after cranioplasty. It should be noted that restoration of normal intracranial physiology is also observed with implants made from other materials than hydroxyapatite,[17] including autologous material.[16]

Osseointegration of CustomBone Implants

The osseointegration properties of hydroxyapatite have been shown in numerous studies.[24,26-32]

In our 30 patients, bone bridges were found between the edges of the implant and surrounding bones. The implant is probably attached and stabilized thanks to neoformed bone tissue, which appears on cross-section and 3D images of the bones obtained by CT scan. Symmetry can also be monitored on CT scans.

Hardy et al.[11] created a scale ranging from 0 to 5 to assess the extent of osseointegration, where 5 was defined as complete osseointegration. However, in our observations, complete osseointegration of the implant did not occur in any of the patients, even 10 years after surgery, but this means that a longer period is necessary to document a complete reossification process.

The porous structure of the implant can still be observed on cross-sectional images of the bones in the patient with a long follow-up, which confirm that >10 years are needed for complete osseointegration. On the contrary, signs of bone formation and osteoinduction appear rapidly 3–6 months after cranioplasty, without inflammation or infection, as already observed in our experience and reported in the literature.

We are aware that the postoperative multiple CT scans can be a problem in very young patients, but most of the time examinations were not to control the integration of the implant but to follow the evolution of cerebral lesions related to the initial pathology of the patient.

Cranioplasty should not be performed until CSF disorders and cerebral edemas have fully healed. When CSF pseudomeningocele, increased volume of subdural CSF, or hydrocephalus are not controlled, it is better to drain the CSF accumulation and to treat

Figure 6. Long-term cosmetic results. (**A**) Two-year postoperative results of a girl operated at the age of 8 months for a right fronto-parieto-temporal craniectomy after trauma. (**B**) Preoperative and (**C**) postoperative results at 5 years after implantation. (**D**) Six year postoperative results on a girl operated for bifrontal craniectomy.

hydrocephalus to favor the closure of the cranium. Without the control of CSF accumulation, it is difficult to put the CustomBone in place, and postoperative intracranial hypertension may appear. In case of tumoral, vascular, or traumatic lesions, cranioplasty should be performed as early as possible after the initial event, when all the edematous phenomena are over so the risk of complications is low without technical difficulties. In case of infectious osteitis, cranioplasty should be performed at least 1 year after the bone flap discard to avoid a recurrence of the infectious foci. In our experience, and contrary to the Beauchamp et al. report in 2010,[33] delayed reimplantation does not increase the risk of complications.

Unlike Hardy et al.,[11] we did not observe neo-ossification below the implant, but we think the use of a Gore-Tex dura mater substitute with no osteogenic properties, in our experience, avoids neoformation of bone.

Ease of Use

Implant installation is simple. The time between ordering of the implant and its delivery to the hospital was relatively short, usually <2

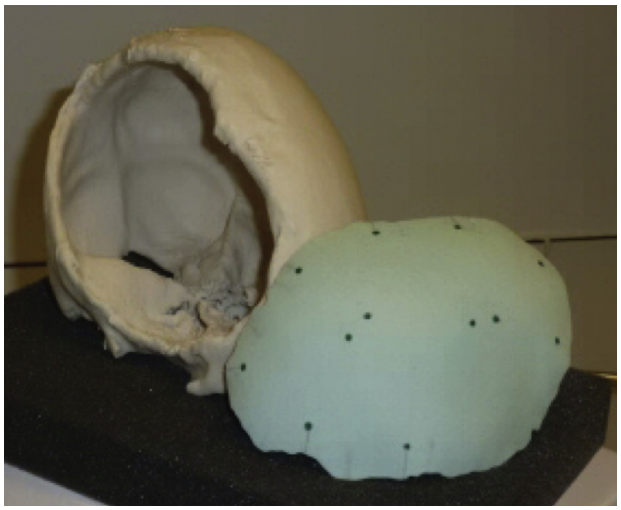

Figure 7. Three-dimensional model of the implant based on a computed tomography scan.

months. Generally, the surgeon can correct its imperfections on the preoperative model. It is possible to build a model with the possible resection of the adjacent bone structure to facilitate the construction of the implant and its inclusion in the cranial defect. The reconstruction of the bone to be discarded is also possible as its reconstruction so the surgeon can have the model during the surgical procedure (Figure 8). The exchange between the surgeon and the manufacturer through the Internet permits the obtainment of models that can be implanted in the operative theater with precision.

Preparation time in the operating room was short. It is advised to let the implant soak in a rifampicin solution for 30 minutes before implantation; this procedure lowers the risk of infectious

Figure 8. Three-dimensional model of the bone edges to remove before the implantation of the implant.

complications. This protocol is suggested by the manufacturers and was approved by our local infection committee and associated with a classic preoperative antibiotic intravenous prophylactic protocol used, in our hospital, for every surgical procedure. The absence of infectious complications in this series does not excluded that, with a larger number of patients, postoperative infection can occur.

Limitations of CustomBone

The main limiting factor is the €8000 price tag for 2 copies of the implant delivered in sterile packaging. Moreover, according to a French study, the use of hydroxyapatite implants is at least €3945 more expensive than using autologous implants.[34] We can ask the question if the lower rate of complications, good aesthetic results, and tolerance observed with these implants can justify the use of a prothesis with such a high cost. We can only comment that the use of these implants has spared the cost of multiple hospitalizations to have a good aesthetical result. In France, we have to justify the economic increase of medical expenses to the authorities.

The Haute Autorité de Santé (the French organization responsible for health care regulation and accreditation) and the Comission nationale d'évaluation des dispositifs médicaux et des technologies de santé (the French committee responsible for the assessment of medical devices and health technology) have laid down rules regarding the use of CustomBone implants:

Custom bone substitutes for cranioplasty are indicated, if there is prior agreement between patient and doctor, in cases where former attempts at autologous grafting have failed, or where the loss of cranial bone substance amounts to more than 35 cm^2 in size and/or is located in the anterior/frontal or frontotemporal region of the skull. In all cases, cranioplasty should only be performed in patients with good neurological or cancer prognosis. (Haute Autorité de Santé, notice of the Comission nationale d'évaluation des dispositifs médicaux et des technologies de santé, January 28, 2014).

The indications are more flexible in the pediatric population, mainly for large bone defects or in case of bone flap resorption. A recent review has reported a lower rate of complications and better aesthetical results in a group of patients treated with a bone substitute, with a success rate of 90%.[35,36] The rate of bone resorption operated with autologous bone tissue ranges from 21% to 80%,[35,37-39] and generally the risk of bone resorption increases in younger aged patients.[36]

Repairing large curved lesions, for instance after bifrontal craniectomy, can be problematic in small children with CustomBone because it is technically difficult to build an implant with a large curve. In such cases, reconstruction is performed using a 2-part implant rather than a single implant because a large curve does not allow the prosthesis to have enough resistance. In these cases, we preconized to build a step between the 2 models on the midline to facilitated the synthesis of the 2 parts with sutures.

Finally, we do not recommend the use of CustomBone or others synthetic implants for reconstruction of the skull base. In these cases, after trauma or tumor, the use of autologous bone is, in our

opinion, absolutely necessary to avoid a high rate of infectious complications and CSF leakage.

CONCLUSIONS

Our experience shows excellent results by using CustomBone implants in the treatment of cranial bone defects in children of every etiology. We do not recommend its use in the reconstruction of bone defects of the cranial base. These implants effectively protect the brain, help to restore normal intracranial physiology, provide satisfactory cosmetic results, and provide rapid clinical recovery, facilitating the inclusion of patients in rehabilitation programs.

Cranioplasty using the original bone flap or autologous bone tissue should be the first option. When an alternative is necessary for cranioplasty, CustomBone implants could be considered by pediatric neurosurgeons. These implants represent an innovative alternative for reconstructive surgery, with satisfactory cosmetic results thanks to lithography techniques, with a more physiologic concept because the osteoinductive properties favor the colonization of autologous bone with the goal to restore closure of the skull with true autologous bone tissue.

Current prices are, in our opinion, justified by the quality of the implant and good clinical results. Even though initial costs are high, we are convinced that in the long term, the use of these implants contributes to reduced costs by eliminating the need for additional surgical interventions and hospitalizations to improve the quality of aesthetical results. Moreover, the improvement of patients' quality of life will lead to better integration at school and in society and lower patient and family anxiety related to eyes of others on the patient.

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