Childs Nerv Syst (2017) 33:343–348
DOI 10.1007/s00381-016-3327-4

ORIGINAL PAPER

Hydroxyapatite ceramic implants for cranioplasty in children: a single-center experience

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Received: 9 September 2016 / Accepted: 15 December 2016 / Published online: 24 December 2016
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Abstract
Purpose The use of hydroxyapatite ceramic (HAC) implants for the treatment of skull defects in pediatric patients started 2010 at our institution. Ceramic implants facilitate osteoblast migration and therefore optimize osteointegration with the host bone. The purpose of this study is to report a single-center experience with this treatment modality.
Methods A retrospective review of all patients from July 2010 through June 2014 undergoing a cranioplasty using hydroxyapatite ceramic implant and managed at a single institution was performed. Indication for cranioplasty, the hospital course, and follow-up were reviewed. Bone density was measured in Hounsfield Units (HU) and osteointegration was calculated using Mimics Software® (Mimics Innovation Suite v17.0 Medical, Materialize, Leuven, Belgium).
Results Over the 4-year period, six patients met criteria for the study. Five patients had an osteointegration of nearly 100%. One patient had an incomplete osteointegration with a total bone-implant contact area of 69%. The mean bone density was 2800 HU (2300–3000 HU). Bone density alone is estimated to have a Hounsfield value between 400 and 2000 HU depending on the body region and bone quality. There were no major complications, and the patients were highly satisfied with the esthetical result.
Conclusion Hydroxyapatite ceramic implants for cranioplasty in pediatric patients are a good choice for different indications. The implants show excellent osteointegration and esthetical results.

Keywords Pediatric · Hydroxyapatite · Cranioplasty · Hounsfield unit · Osteointegration

Introduction

Cranioplasty is a neurosurgical intervention that replaces a defective or missing part of the skull. Nowadays, mainly three different techniques of cranioplasties are used. One can either graft 1. autologous bone, 2. synthetic material, or 3. bioprosthetic material. All three modalities have the same goal by protecting the brain against injury or infection and to provide a good esthetical appearance. However, there is a big variation in the biocompatibility, osteointegration and finally the satisfactory cosmetic result [1–5]. Autologous bone grafts are still considered the gold standard for the repair of skull defects due to its favorable biological properties [6–8]. This method is particularly ideal in the pediatric population for its greater reintegration potential of the graft during skull growth [4, 9]. Nevertheless, the use of autologous bone grafts may harbor some risks. Furthermore, the use of an autologous bone fragment from the contralateral side of the skull may cause a "harvesting defect" with increase in bone resorption. In other cases, the skullcap cannot be reconstructed or preserved for re-implantation due to trauma with multi-fragmentary skull fractures, contamination at time of injury or in cases with tumor infiltration of the skull [1, 2, 6, 10].

Several different synthetic materials were developed in the past to overcome these problems. Currently, materials like polymethylmethacrylate (PMMA), porous polyethylene, polyetheretherketone (PEEK) or titanium are used. They can be shaped and modeled to a certain degree in the operating

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room or they can be produced before surgery based on computed tomography (CT) models of the patient with the help of computer-aided design and computer-aided manufacturing (CAD/CAM) programs. A considerable disadvantage of these materials is that they do not show optimal osteointegration, and they have to be fixed to the native bone with plates or screws.

A promising characteristic of bioprosthetic materials like hydroxyapatite ceramic (HAC) is its similar chemical composition compared to human bone [6, 10]. The porous property of HAC facilitates osteoblast migration and thus an optimal ossification process and integration of the prosthesis with an excellent stability without formation of scar tissue [1, 11].

The aim of this paper is to present a single-center experience of a tertiary pediatric neurosurgery hospital with the use of HAC for cranioplasty for various indications.

Material and methods

Data collection

This is a retrospective review of patients from July 2010 to June 2014 who underwent cranioplasty with custom-made hydroxyapatite ceramic (HAC) implantation (CustomBone Service™, Fin-Ceramica Faenza S.p.A., Italy) for various indications and were treated at the University Children's Hospital Zurich. This study was approved by the Ethics Committee (2016–00043).

Surgical procedure

According to a standardized protocol the CustomBone device is obtained by processing a 3D CT-scan of the skull, and then produced by a manufacturer in northern Italy (Fin-Ceramica Faenza S.p.A., Italy) [3]. The implant is then tested with respect to shape and size on a model (Fig. 1). The manufacturing and testing process takes 3–6 weeks.

All patients receive a perioperative single-shot prophylaxis with cefazoline. The sterilized HAC implants are treated in a gentamicin solution (40 mg gentamicin, Ratiopharm, Ulm, Germany/100 ml NaCl 0.9%, B. Braun Medical AG, Sempach, Switzerland) prior to implantation. The HAC implant is then used to cover the skull defect and is anchored to the bone with absorbable sutures (PDS II 1–0, Ethicon, Sommerville, USA). Additionally, a "hitch stich" in the center of the implant to the underlying dura (PDS II 5–0, Ethicon, Sommerville, USA) may help to prevent forming an epidural hematoma. The implant-bone junction is occasionally sealed with fibrin glue (Tisseel, Baxter, International Inc., Westlake Village, USA). In some cases a subgaleal drain was placed for 24–48 h postoperatively. The subcutaneous tissue and skin are closed in the usual fashion. In patients with a benign skull tumor, the bone defect was covered during the same operation after removal of the tumor. The tumor resection was assisted by CT navigation control. In patients with a congenital defect (Catlin marks) and traumatic brain injury (TBI), the bone margins were refreshed by sharp debridement before primary or secondary implantation respectively.

Follow-up CT-scan

A follow-up CT-scan of the skull was performed between 9 and 40 months (mean 26.5 months) postoperatively to document the ingrowth as well as the osteointegration process. The bone density was measured according to the Hounsfield scale in different areas of the implant (Fin-Ceramica Faenza S.p.A., Italy, Table 2 and Fig. 2). Overall, the measured Hounsfield values were constant across the whole implant and always higher than in human bone. Therefore, we decided to indicate only the best ingrowth region of each implant by one representative value with the corresponding standard deviation (SD). Osteointegration was calculated and measured using MIMICS software (Mimics Innovation Suite v17.0 Medical, Materialize, Leuven, Belgium).

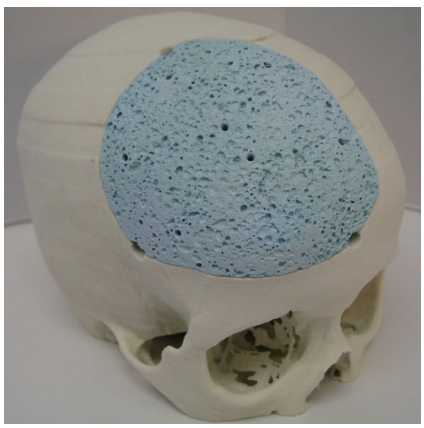

Fig. 1 HAC implant model

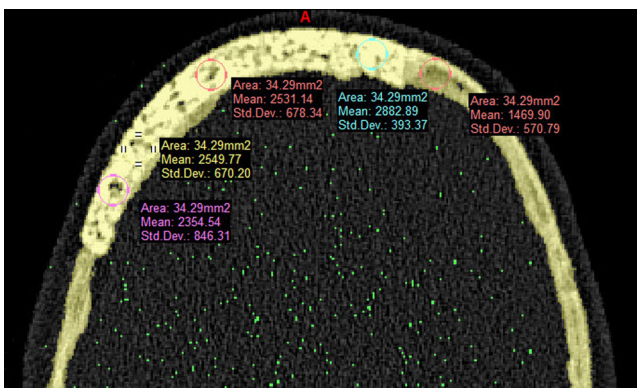

Fig. 2 Measurement of bone density according to the Hounsfield scale in different areas of the implant and bone

Table 1 Synopsis of patients undergoing HAC implantation

Patient	Diagnosis	Age at surgery (years)	Affected bone surface (cm^2)	Indication for HAC implantation	Surgical technique
Case 1 (f)	Juvenile psammomatoid ossifying fibroma of the forehead	11.4	66.85	Increasing size of the tumor with mass effect on brain and displacement of the anterior horn	Craniectomy and radical en bloc resection of the tumor and coverage with HAC composite according to in-house protocol
Case 2 (m)	Basal skull fracture Ischemic stroke due to traumatic carotid artery-dissection	7.5	117.81	Fracture and dislocation of the bone cement implant previously used after decompressive craniectomy	According to in-house protocol
Case 3 (m)	Bilateral parietal foramina (Catlin marks)	9	4.02 (right) 3.15 (left)	Cosmetic reason	According to in-house protocol
Case 4 (m)	Impaling brain injury	7.1	113.09	Autolysis of autologous bone fragments and infection of previously used Titan-mesh	According to in-house protocol
Case 5 (f)	Non-involuting congenital hemangioma (NICH) on right frontal bone 22q11 Syndrome Double outlet right ventricle (DORV)	9.5	66.21	Growing tumor and intracranial expansion	1. Embolization of feeding vessels of tumor 2. Resection of tumor and HAC implantation according to in-house protocol
Case 6 (f)	Depressed right temporo-parietal skull fracture	13.9	33.78	Multiple fractured bone fragments	According to in-house protocol

HAC Hydroxyapatite ceramic, *f* female, *m* male

Results

During the study period, six children (three females and three males) between the age of 7 and 14 years (mean age 9.6 years), were treated at our tertiary referral hospital with a HAC implant (CustomBone Service™, Fin-Ceramica Faenza S.p.A., Italy) for different indications (Table 1). Two children showed a benign proliferative neoplastic lesion (case 1, Fig. 3a, b), one child had congenital bilateral parietal foramina (Catlin marks) and the remaining three patients suffered from a TBI.

Generally, all cases showed an uneventful postoperative course after HAC implantation, except for case 5. Due to the patient's cardiac disease, an antithrombotic prophylaxis was started 4 days after surgery. She developed a subgaleal hematoma at the operating site, which had, to be evacuated subsequently. The further postsurgical course was uneventful. A follow-up head CT-scan was performed in all children between 9 and 40 months (mean 26.5 months) postoperatively. An optimal osteointegration of 98–100% was achieved in five of six children. In all six patients, the mean Hounsfield scale ranged between 2300 and 3000 HU depending on the porosity of the HAC implant (Table 2).

The esthetical outcome at follow-up was judged on a subjective basis by the patient, the parents and the surgeon as excellent in five patients (83%). The surgeon noticed a slightly asymmetrical forehead due to some osseous protrusion in the patient that

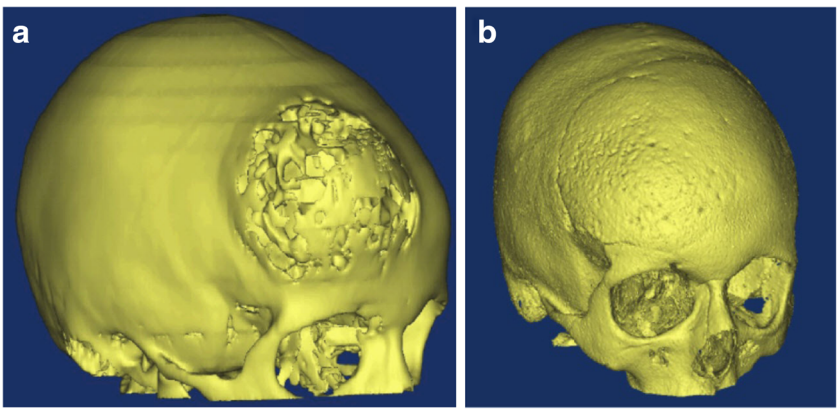

Fig. 3 **a** Patient with a juvenile psammomatoid ossifying fibroma of the forehead (case 1) before HAC implantation. **b** Follow-up CT-scan 40 months after tumor resection and HAC implantation showing an excellent osteointegration and cosmetic result

Table 2 Follow-up and cosmetic result of patients undergoing HAC implantation

Patient	Cosmetic result	Time to follow-up CT (months)	Osteointegration at margin (%)	Density ± SD (HU)
Case 1 (f)	excellent	40	98.3	2882.89 ± 393.37
Case 2 (m)	excellent	26	100	2387.33 ± 260.91
Case 3 (m)	excellent	34	100 on each implant	2926.02 (right) ± 271.46 2809.18 (left) ± 492.24
Case 4 (m)	Very good	29	69	2811.28 ± 419.79
Case 5 (f)	excellent	21	100	3064.48 ± 39.2
Case 6 (f)	excellent	9	98	2906.54 ± 329.39

HAC Hydroxyapatite ceramic, *f* female, *m* male; *SD* standard deviation, *CT* computed tomography, *HU* Hounsfield units

initially had an impaling brain injury (case 4). However, this asymmetry was noted neither by the patient nor the parents. They were very satisfied with the cosmetic result.

Discussion

The use of HAC compounds for the repair of cranial defects has only been described in the last 25 years. Over the years, this modality has been optimized and currently customized implants for the patients can be used. Nevertheless, the literature on HAC implants in the pediatric population is scarce. We report our experience with HAC at our tertiary pediatric neurosurgery center for various indications.

Autologous bone graft is still considered the first choice for repair of skull defects in the pediatric population [7, 8, 12]. However, there are some problems and complications reported. The main problem is the high complication rate after re-implantation of the autologous bone graft which includes bone flap resorption and infection in children less than 7 years of age, making surgical revision necessary [5, 9, 13–17]. Literature reports a risk of up to 40% for infection or autolysis with autologous bone grafts being used for cranioplasty [18]. In addition, the skullcap cannot be reconstructed or preserved in cases with multi-fragmentary skull fractures, contamination of the bone at the time of injury or tumor infiltration of the skull [1, 2, 6, 10]. Furthermore, a lack of fusion and an unsatisfactory esthetical result can occur if the dimension of the operculum does not match the size of the craniolacuna [10].

The ideal graft material for a cranioplasty must meet certain important criteria: It has to be biocompatible, mechanically resistant and inert in order to prevent inflammation, rejection or infection. Furthermore, it has to show an optimal osteointegration, and it should result in a satisfactory cosmetic result for the patient [1, 2, 4]. Different synthetic materials such as titanium, acrylic cement (PMMA) and pre-shaped polyetheretherketone implants (PEEK) have been used widely in the past. The former two are easily moldable and may be rigidly fixed to the cranial bone [19–21]. Titanium is known to cause a foreign body sensation and may lead to psychological problems regarding the patients' acceptance of the implant [22]. The polymer products on the other hand are known to have a high failure rate due to their significant inflammatory response. The resulting exothermic reaction can potentially cause thermal and toxic injury to the dura mater and brain [16, 19, 22]. Moreover, synthetic materials may be less desirable in the pediatric population as these materials do not grow with the patient and may therefore necessitate further surgery in the future [17, 23]. The literature shows a low rate for re-operation if customized implants like titanium or PMMA are used (4.4% and 9.6% respectively) [10]. The same is true for HAC implants. Stefini et al. report the lowest rate for re-

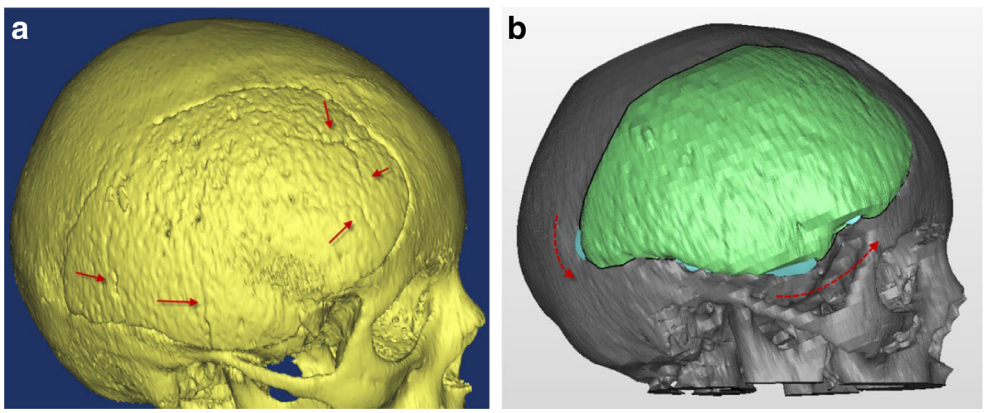

Fig. 4 **a** The *red arrows* indicate the different fracture zones in the area of the HAC implant after minor head trauma. **b** The implant shows a slight anticlockwise rotation of 8°, resulting in an incomplete osteointegration with a total bone-implant contact area of 69%

operation (3.8%) in adults and children over 7 years of age. This is most likely related to the excellent osteointegration [10]. On the other hand, the re-operation rate for moldable calcium-based cements or PMMA is up to 50%, depending on the size of the defect [24]. Autologous bone grafts have also a higher rate (14.9%) compared to customized implants, due to the high risk for infection and autolysis of the bone fragments [10].

Hydroxyapatite ceramic consists to 75% of hydroxyapatite, which is also the main component of human bone. The Calcium/Phosphor ratio of 1.67 is comparable to that of human bone (1.71) [1, 2, 6, 10]. The porous property of HAC facilitates osteoblast migration and results in good ossification and integration of the implant with excellent mechanical stability without formation of scar tissue. This has been demonstrated in animal models and in human studies [1–3, 11, 25, 26]. Hounsfield tensometer graphs in our patients at the time of follow-up CT show continuity between the implant and the host bone with values between 2300 and 3000 HU (SD 39–490 HU; Table 2). These values are much higher than normally seen in human cancellous or cortical bone. This is explained by the higher density of hydroxyapatite itself compared to bone and by the osteoblast migration into the pores. The density of human bone is estimated to be between 400 and 2000 HU, depending on the body region and bone quality [27].

As stated above, nowadays the implants can easily be performed based on CT models of the patient. These customized HAC implants can be sutured with resorbable stitches [1, 2, 11, 28]. However, there are also some disadvantages. An emergency coverage of a skull defect is not possible since the development of a HAC implant takes actually between 3 and 6 weeks. Furthermore, the HAC implants are prone to break following minor head injury if an effective osteointegrative process had not occurred yet. For this reason we recommend sports leave for at least 3 months and depending on the course, even longer for contact sports. This has to be noted in preoperative counseling. In general, we do not recommend a helmet postoperatively.

The use of HAC implants in children less than 7 years of age was not recommended at the time of our study. This limitation was due to the prevalent growth of the skull by 5–6 years of age. On the other hand, Frassanito et al. were able to show that HAC implants are effective and safe for children older than 2.5 years of age [8]. In our study group, no patient was under 7 years of age at the time of HAC implantation. Our youngest patient was 7.1 years old.

All but one patient showed an optimal osteointegration of 98–100% without major complications and an excellent cosmetic result. Case 4, the patient with the impaling brain injury had an incomplete osteointegration with a total bone-implant contact area of 69% and several minor fracture zones (seen on a follow-up CT 2 years after HAC implantation, Fig. 4a, b). This was caused by an unobserved fall and minor TBI about 1 year postoperatively. However, no revision was necessary and the clinical follow-up (2 years) to date is uneventful.

We would like to point out that primary HAC implantation can even be considered in children with severe co-morbidities like in our case 5. The patient had a hemangioma (NICH, non-involuting congenital hemangioma) on the right frontal bone, microdeletion 22q11 and severe cardiac disease (Table 1). Interventional coiling prior to resection embolized the feeding vessels to the tumor. The resulting skull defect was primarily repaired with a HAC implant.

There are limitations to our study. The main limitation is inherent in a retrospective review but this study is strengthened by the consistency of a single-institution experience with a consistent protocol. Another limitation is the small number of patients but we were able to demonstrate successful outcomes for a broad range of indications like congenital skull defect, tumor, and traumatic skull fracture.

Overall, the results are encouraging, but to reinforce the meaningfulness for HAC implantation, a prospective multicenter study is needed.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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