A Multicentric European Clinical Study on Custom-Made Porous Hydroxyapatite Cranioplasty in a Pediatric Population

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Background: Cranioplasty (CP) is a surgical intervention aiming to re-establish the integrity of skull defects. Autologous bone and different heterologous materials are used for this purpose, with various reported related complications, especially in children. This study aims to evaluate the rate of complication in a multicentric cohort of pediatric patients treated by porous hydroxyapatite (PHA) CP implantation and to assess the reliability of post-marketing clinical data collected by a manufacturing company.

Methods: The authors proactively collected clinical data from 20 institutions in different European countries for patients under the age of 16 treated with a PHA implant. The data were obtained by conducting an on-site interview with physicians in charge of the patients (Post-Marketing Surveillance, PMS group). The endpoints were the incidence of adverse events and related implant removal. The clinical data were compared to the company-based register including all patients under the age of 16 who received the same implant from January 1, 2004 to December 31, 2020, and the collecting complications voluntarily reported by surgeons (Database, DB group).

Results: The two groups were similar in terms of demographic characteristics and rate of complications. In the PMS group, a total of 11 (16.9%) complications were reported in the group of 65 patients that were proactively collected. Both fractures and infections were the most common complications with 4 cases each (6.2%). In the case of both infections and fractures, revision surgery was required for only one patient (1.5%). Three (4.5%) cases of displacements were reported, and in one (1.5%) case, a surgical revision was required, for a total of 3 (4.5%) cases requiring surgical revision. The average follow-up was 26.7 months.
**INTRODUCTION**

Cranial reconstruction (CR), also known as cranioplasty (CP), is a common neurosurgical procedure usually performed to restore the cranial vault after decompressive craniectomy or any other previous surgical procedure that affected the skull bone, such as that for erosive tumors. Autologous bone remains the gold standard option for cranial reconstruction; however, this option is not always feasible because of storage limitations and high infection risk in the case of open skull fractures. Recent studies have also shown that these limitations of autologous bone cranioplasty are more important in pediatric patients with a higher rate of bone reabsorption (1, 2). In this setting, it is important to correctly define the pediatric population (3). Children present clinical characteristics that are different from those of the adult population: the growing and dynamic bone remodeling present in kids suggests different surgical outcomes and leads to limitations in the usage of various materials (4). Also, a stratification of age range could be helpful in clinical management and decision (4, 5).

To overcome the limitations of autologous cranioplasty in children, several heterologous materials have been developed recently such as porous hydroxyapatite (PHA), titanium, polyetheretherkone (PEEK), and polymethylmethacrylate (PMMA) (6).

To date, there is still little evidence concerning the optimal material selection for cranioplasty in the pediatric population (3, 7). Among the most recent materials, PHA cranioplasties have gained popularity because of their particular biochemical characteristics that allow for osteointegration with the skull bone. Despite this interest, there are only a few studies that evaluate the use of such devices in the pediatric population.

Furthermore, several complications may occur after PHA cranioplasty in children, such as hematoma, hydrocephalus, displacement, fracture, and infections (8, 9). Two types of complications are identified: (a) related to the procedure itself, and (b) related to the implant material.

In this study, the authors evaluated cranioplasty complication rate in a multicentric cohort of pediatric patients who underwent PHA cranioplasty, and compared these results with a company post-market clinical analysis to see the reliability of self-reported complications by surgeons in the field of pediatric cranioplasty, as previously performed on the adult population (6). Lack of reported complications to the manufacturing company makes it difficult to compare these reports to any other study published by neurosurgical centers.

**Conclusions:** Different from a previous study on adult age, pediatric neurosurgeons are more prone to report even to the manufacturing company complications related to skull reconstruction in children. Therefore, these data can be compared with those of other clinical studies. The PHA CP in this series of 65 patients presents a complication rate collected on-site that is similar to other heterologous materials.

**Keywords:** cranioplasty, cranial reconstruction, porous hydroxyapatite, pediatric, cranioplasty complication

**MATERIALS AND METHODS**

The study includes patients below the age of 16 years who underwent PHA cranioplasty (CustomBone Service, Finceramica Faenza Spa, Italy).

To achieve the goal of the study, the complication rate in two groups of pediatric patients was compared: the first group included all PHA custom bone implanted patients from Custom Bone Service Fin-Ceramica, Faenza Database; whereas in the second group, a randomly collected group of patients from European Neurosurgical Centers underwent clinical follow-up.

Details about the surgical methodology were already published elsewhere (6). The current European Medical Device Regulation requires post-market clinical follow-up activities to be carried out by manufacturers to evaluate device performance and safety. For CustomBone Service, the activity of post-market clinical follow-up started in December 2018 (10). For this activity, a specific protocol and a case report form (CRF) were produced for data collection. The protocol is included in the Supplementary Material.

Among all institutions using custom-made PHA, 20 neurosurgical European centers have been randomly contacted for data to analyze their experience with this device in pediatric patients. Each center participating in the study was visited by one of the co-authors (IZ) before the coronavirus disease-2019 (COVID-19) restriction period, and CRFs were filled for each patient implanted in the institution with the aid of neurosurgeons involved in the procedure (Supplementary Material). The centers involved in this study are summarized in **Table 1**.

Concerning the use of the database from the manufacturing company, an agreement was reached to allow the authors to use the company database for scientific purposes. The database is web-based, and it contains general information, under a serialized number for privacy purposes, of all patients implanted with a PHA cranioplasty. The company agreed not to influence the collection of data, and the results of the study were not available to the company before study publication.

Several variables were taken into consideration for this study, namely, demographic information (gender, age, and surgery date), initial pathology, reason for surgery, localization of the cranial lesion, date of surgery, and country. Concerning postoperative outcome, the authors collected all main types of complications related to PHA cranioplasty implantation (deep and superficial infection, device fracture or mobilization, or related to the procedure, i.e., hydrocephalus, epidural, or subdural hematomas). Finally, an explantation and follow-up data were also collected.
TABLE 1 | Centers involved in the study.

| Country   | City          | Hospital                                           |
|-----------|---------------|----------------------------------------------------|
| Belgium   | Ghent         | Ghent University Hospital                         |
| France    | Paris         | Hôpital Lariboisière                              |
|           | Strasbourg    | Hôpital de Hautepièrre                            |
| Italy     | Alessandria   | Ospedale SS. Antonio e Blagio e Cesare Arrigo     |
|           | Aosta         | Ospedale Regionale della Valле D’Aosta            |
|           | Bologna       | Bellaria Hospital                                 |
|           | Maggiore      | Maggiore Hospital                                 |
|           | Brescia       | Spedali Riuniti                                   |
|           | Gemona del Friuli | San Michele Hospital                          |
|           | Naples        | Santobono hospital                               |
|           | Padua         | Ospedale Civile                                   |
|           | Palermo       | Policlínico Universitario                         |
|           | Parma         | Maggiore Hospital                                 |
|           | Perugia       | Santa Maria della Misericordia                    |
|           | Rome          | Bambino Gesù Children's Hospital                  |
|           | Rozzano       | Humanitas Research Hospital                       |
|           | Udine         | Santa Maria della Misericordia                    |
|           | Vicenza       | San bortolo hospital                             |
| Switzerland | Lausanne     | Centre Hospitalier Universitaire Vaudois          |
| Ireland   | Dublin        | Temple street children's hospital                 |

Statistical Analysis
Continuous variables were analyzed by Fisher’s Exact test. Statistical analyses were performed using the Excel software (Microsoft, Redmond, United States). The P-values were considered significant if <0.05. To define the representativeness of the clinical series compared to the whole population implanted with the CustomBone device, a t-test was performed. A t-value >1.96 was considered significant.

RESULTS
The PMS group comprehended clinical data from 65 pediatric patients below the age of 16 (for a total of 76 implanted devices) that were collected from the different hospitals visited by the authors. Among all, 36 (55%) of the patients were male and 29 (45%) were female, with a mean age of 9.1 years (1–16 years ± 4.67). They were stratified into four different groups based on the age ranges: there was 1 (1.5%) child in the range 0–2 years old, which has been implanted off-label, 18 (27.7%) children between 2–7 years old, 25 (38.5%) of them were included in the range 8–12 years old, and, finally, 21 (32.3%) patients were in the last group (12–16 years).

The DB group included data from 725 patients (below the age of 16), who received a CustomBone device from January 1, 2004 to December 31, 2020. The majority of devices (98%) were implanted in Europe, mostly, in France, Italy, and Germany.

The comparison between the two groups is summarized in Table 3. Results of the PMS group were further detailed.

PMS vs. DB Group
As reported in Table 2, there was no statistically significant difference in terms of gender (t = 1.142), cause of decompression (t = 1.012), or line of treatment (first or second line of treatment) (t = 1.457). On these grounds, the series of patients proactively collected has been considered representative of the whole implanted pediatric population (Table 2).

Different from the study performed on the adult population (6), the revision rate (t = 0.7433) and explantation rate (t = 0.5106) between the two groups were not significantly different, making the data obtained by self-reporting neurosurgeons
in pediatric cranioplasty reliable. Similarly, the rate of complications is summarized in Table 4.

**PMS Group**

Regarding the etiology of the defect, the majority of pediatrics included in the PMS group were affected by traumatic brain injury (n = 39, 60%), while a minority of them also presented with other different issues. In particular, 7 (10.8%) children presented with tumors invading the skull, 6 (9%) of them had vascular pathology, while 6 (9%) others had a congenital malformation. The remaining was presented with infections (3.1%) or other minor pathologies (7.7%). There was no significant correlation between the etiology of the cranioplasty and postoperative surgical outcome.

Forty-three (66%) patients received PHA implantation as the first-line of treatment, while in 22 children (34%), cranial reconstruction was performed as a second-line procedure after the failure of the previous cranioplasty. The patients who received PHA cranioplasty as a second-line treatment were slightly but significantly more prone (p = .043) to have postoperative infections. However, no correlation was found between the line of treatment and revision rate.

The site of defect was most frequently fronto-parieto-temporal (n = 25, 38.5%), but a great number presented also in the frontal (n = 13, 2%) and bifrontal 10 (15.4%) regions. A minority of them were referred for cranioplasty in the frontoparietal (n = 4, 6.2%) and parietal temporal (n = 5; 7.7%) regions. Finally, 2 (3.1%) patients had localization in the parietal area, and 2 (3.1%) of them in the crown area (Table 3). No correlation was found between the location of the cranial implant and postoperative risk of infection or fracture. Considering the dimensions of the implants, the mean dimension was 22 ± 13 cm². In the 65 patients considered, there was no correlation between the dimension of the cranioplasty and postoperative infections.

Overall, a total of 11 (16.9%) complications were reported in the cohort of 65 pediatric patients. Both fractures and infections were the most common complications reported with 4 cases each (6.2%). In case of both infections and fractures, revision surgery was required only in one case (1.5%). Three cases of prosthesis displacements (4.6%) were reported, with one surgical revision (1.5%) required. As such, only 3 cases (4.5%) required surgical revision (Table 4). The average follow-up was 26.7 months.

**DISCUSSION**

The autologous bone flap is the gold standard material for cranial reconstruction due to its characteristics of durability, accessibility, elasticity, low economic costs, and biocompatibility (11). The most common donor areas for autologous bone are the cranium, ribs, and iliac crest. The advantages of using autologous bone include, among others, minimal dislodgement or disintegration due to a higher rate of revascularization and integration with adjacent bone (7, 12). Unfortunately, autologous bone cranioplasty is burdened by a high complication rate, with a risk of bone reabsorption or infection of the autologous flap as high as 51% under 18 years of age (13). This rate is even higher if a lower age threshold is used to define the pediatric population, the risk decreasing linearly with the age of patients (4).

Whenever an autologous bone is not available, several heterologous materials have been proposed in cranial reconstruction, although the level of evidence reached by literature data on the use of these implants remains extremely low, especially in children (7). Thus, a careful evaluation should be made by physicians to choose the appropriate device based on the characteristics of patients.

Among the different options present on the market, one of the most recent is porous hydroxyapatite cranioplasty, which aims to
improve biomimetic assimilation using, as the main constituent, a human mineral bone component (12).

Despite significant evolution of the materials and technology used for cranial repair, in the pediatric population, specific additional limitations may occur because of the active stage of growth and development of the cranial vault (14). In a recent systematic review, the overall rate of pediatric CP complications with different synthetic materials was reported to be about 14.2% (7). Titanium graft is reported to have an overall lower complication rate (6.7%) than polymethylmethacrylate (PMMA) and PEEK. The PEEK presents the highest infection rate (16.1%), while PMMA presents a 10.9% total rate of surgical site occurrence: a surgical-site infection rate of 10.9 and 16.4% of graft failure (15). However, the results of different studies are difficult to be compared because of a lack of homogeneity, in particular, concerning the age of patients included in the study (16). Indeed, the demography of case series in the literature presents a large spectrum of cut-off between the pediatric and adult populations, ranging from 13 to 19 years old (4, 5). Recent investigations have shown that cranial development reaches 80% growth at 2 years old, while at 5 years old it is complete for the 90%, allowing for correct brain development (3). Consequently, a critical analysis of the outcome and complications of CP requires proper age stratification of patients. However, the study by Klieverik et al. showed that data in the literature do not show detailed and specific comparable outcomes in children (7). Therefore, long-term follow-up studies on heterologous cranioplasty in the pediatric population would be necessary, with subgroup analysis for specific complications and age stratification to critically compare the results of CP in the pediatric population.

On these grounds, custom-made porous hydroxyapatite showed to be an option for pediatric CP, and literature data allow for stratification of complications by age for PHA implants, with a rate of explantation of 20.8% under 7 years of age, and 6.58% in the group 7–13 years of age (1, 17, 18).

In this study, the main complications reported were fractures (6.2%) (Figure 1), together with infections (6.2%) and displacement (4.6%). In total, 3 (4.5%) surgical revisions were performed.

The rate of fractures in our study is lower than that in other published clinical series (16, 19). This difference in complications could be explained by different factors, among which is a change in the HA cranioplasty manufacturing process. In the beginning, the median porosity of the prosthesis was up to 70% (20), whereas later, it did not exceed 50% (2). Changes were because the presence of porosity allows for better integration with the cranial vault, but it also makes cranial implants more fragile. Therefore, neurosurgeons need to be aware that until a possible bone integration occurs, HA cranioplasty is more fragile than other heterologous materials. Another complication that is worthy of further analysis is a higher rate of displacement compared to the one seen in the clinical series studying other materials (4.6%). In general, heterologous cranial implants are fixed through screws and plates, but this is not possible in the case of PHA cranioplasty because of the risk of prosthesis fracture using screws. Normally, these prostheses are secured with the use of silk sutures through prefabricated holes in implants and this can cause higher mobility of the implants.

Also, causes of the initial pathology resemble the common ones in the literature (21, 22): trauma (60%), tumors (10.8%), vascular (9.2%), malformations (9.2%), infections (3.1%), and others (7.7%). The overall complication rate (16.9%) is similar to what was reported by Klieverik (7).

Furthermore, the present rates of complications and explantation (16.9 and 4.5%, respectively) are comparable to the rates previously reported in children 7–13 years old (14.5 and 6.58%, respectively) (1).

Moreover, the rate of explantation (4.5%) is similar to the rate recently reported in a large adult series of PHA CP (4.25%) (6), although the present study also included patients under 7 years of age at higher risk of complications (23).
The 65 pediatric cases reported here were randomly collected from 20 clinical sites. These cases were treated in most recent years but show similar clinical features of the total pediatric population collected by the manufacturer’s database, as confirmed by the comparison between the two groups. The two cohorts of patients were indeed comparable in terms of age, gender, cause of decompression, line of treatment (first- or second-line of treatment), revision rate, and explantation rate (24–26).

Another interesting finding of our study is that different from the adult population (6), the rates of complications in the two groups almost correspond. In our adult series, the complication and explantation rates were almost double in the on-site collected data compared to the company database. This would reasonably fit with higher attention in surveillance and reporting of complications in children by neurosurgeons.

**Study Limitations**

Despite the authors’ best efforts, this study presents some limitations. One of them is the lack of control comparison of the outcomes among the several synthetic materials used in the cranial reconstruction. Furthermore, the data regarding the timing of cranioplasty, patients’ clinical status at surgery, and the presence of systemic infections were not available.

**CONCLUSIONS**

Our results suggest that pediatric neurosurgeons are more prone to report complications to the manufacturing company; therefore, these data can be directly compared with clinical studies. The complication rate of HA cranioplasty in children age in our series is similar to other heterologous materials. Further clinical comparative studies on heterologous materials in the pediatric age are needed.

**DATA AVAILABILITY STATEMENT**

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

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**ETHICS STATEMENT**

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent to participate in this study was provided by the participants’ legal guardian/next of kin. The requesting doctor declares and certifies that the patient, or another individual legitimately authorized to represent the patient, has given specific information concerning the gathering and handling of personal and sensitive data indicated in this request and the accompanying medical documentation needed for designing, producing, supplying, and post-supply surveillance of the custom-made device in porous hydroxyapatite. Moreover, the requesting doctor declares and certifies that the patient, or other individuals legitimately authorized to represent the patient, has given express consent for the handling of the personal data indicated and for the aforementioned purposes, even by the company involved in the designing, producing, supplying and post-supply surveillance of the device, as well as companies and/or organizations collaborating in the procedure for designing and producing the device proper. Lastly, the requesting doctors declare and certifies that the patient, or other individuals legitimately authorized to represent the patient, has given express consent for the use of the clinical data gathered for scientific purpose.

**AUTHOR CONTRIBUTIONS**

FS and IZ: conception. IZ and AS: data collection. All authors: manuscript drafting. All authors contributed to the article and approved the submitted version.

**SUPPLEMENTARY MATERIAL**

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fsurg.2022.848620/full#supplementary-material
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