Long-Term Series of Custom-Bone Hydroxyapatite Cranioplasty: Outcomes and Survival at 15 Years

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Introduction: Cranioplasty (CP) is a surgical procedure used to repair or reconstruct bone defects in the skull. As CP is not without risk, identifying the safest reconstruction technique is essential to achieve optimal functional recovery. While heterologous prostheses such as HA address issues related to storage and preservation of autograft and help prevent bone resorption, they are associated with a specific spectrum of risks, including infection, dislocation, and fracture. The aim of our article is to evaluate the safety and performance of HA cranioplasty through a retrospective study conducted at 2 centres with extended follow-up of up to 15 years. This study represents one of the most comprehensive and long-term analyses available and provides important insights into the efficacy of this material in clinical practice.

Methods: Data were collected from patients who underwent CP between December 2001 and December 2008. The authors conducted a retrospective study of a case series of 101 adult and paediatric patients who received custom-made HA implants after craniotomy for various reasons. The primary endpoint was to evaluate prosthesis survival and explantation rates. Secondary endpoints included the incidence of adverse events and the rate of surgical revision.

Results: Over a period of 7 years (from December 2001 to December 2018), a total of 101 patients who underwent CP with custom-made HA prostheses. Skull reconstruction with CP was performed immediately in 22 cases. All patients were initially evaluated 30 days after CP, with subsequent follow-ups at 6 months, 12 months, 24 months, and then at 3, 4, 5, 10, and 15 years. Major complications requiring explantation were observed in 9 patients: The reasons for explantation were as follows: 3 cases of infection, 2 cases of tumour recurrence, 2 cases of fracture, 1 case of cicatrial retraction, and 1 case of cerebral hemorrhage. Minor complications occurred in 10 cases and resolved without the need for explantation of the HA prosthesis. At the 15-year follow-up, radiographic and clinical evaluations of 41 patients confirmed optimal results, with complete and stable integration of the implant into the surrounding bone and no significant resorption or migration.

Conclusions: This study provides a comprehensive long-term evaluation of custom HA CP, providing valuable insight into its efficacy and safety over a 15-year follow-up period. Our findings support the viability of HA as a material for cranial reconstruction, demonstrating a high prosthesis survival rate with stable integration in the majority of patients.

Key Words: Cranioplasty, HA, hydroxyapatie, long term

(*J Craniofac Surg* 2025;36: 1263–1266)

Cranioplasty (CP) is a surgical procedure used to repair or reconstruct bone defects in the skull that may result from trauma, previous neurosurgical procedures, congenital deformities, or tumor resection.[1] The primary goal of the procedure is to restore the structural integrity of the skull while protecting the underlying brain tissue. It also aims to restore cosmesis, facilitate neurological rehabilitation and normalize cerebrospinal fluid hemodynamics and metabolism.[2]

As CP is not without risk, identifying the safest reconstruction technique is essential to achieve optimal functional recovery. A variety of materials are used in CP, including metals such as titanium, synthetic materials, such as polymethylmethacrylate (PMMA) and polyetheretherketone (PEEK), and biological materials such as autologous bone and hydroxyapatite (HA). Each material has its own benefits and challenges.[3]

Biocompatibility, availability, mechanical stability, and ease of manipulation are fundamental characteristics of the ideal implant material. It should have osteoinductive and osteoconductive properties, be resistant to infection and be economically affordable. As none of the currently available materials can meet all these criteria, the current choice of material for CP depends largely on the preference of the neurosurgeon and the specific circumstances.[4]

Hydroxyapatite, a calcium phosphate compound, is particularly promising for CP due to its chemical composition [$Ca_{10}(PO_4)^6(OH)^2$], which closely resembles natural bone. This similarity promotes osteointegration and minimizes inflammatory responses. It is a porous material that allows the

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Received October 27, 2024.

Accepted for publication December 14, 2024.

L.V. recived funding from Italian National Ministry of Health. The remaining authors report no conflicts of interest.

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Supplemental Digital Content is available for this article. Direct URL citations are provided in the HTML and PDF versions of this article on the journal's website, www.jcraniofacialsurgery.com.

ISSN: 1536-3732

DOI: 10.1097/SCS.0000000000011061

growth of osteofibrous tissue within it (osteoconductivity) and thus integration with the surrounding bone tissue. The main problem with this material is its high fragility, which lasts for several months, so is why it is sometimes necessary to prioritize primary mechanical strength by using materials such as PMMA or PEEK. Compared with HA, these materials have better compressive and flexural strength and significantly greater elasticity.[5–7]

While heterologous prostheses such as HA address issues related to storage and preservation of autograft and help prevent bone resorption, they are associated with a specific spectrum of risks, including infection, dislocation, and fracture.[8]

Numerous studies have documented the benefits of HA, with long-term follow-up demonstrating its reliability and sustained efficacy over time.[9] The aim of our article is to evaluate the safety and performance of HA cranioplasty through a retrospective study conducted at 2 centers with extended follow-up of up to 15 years. This study represents one of the most comprehensive and long-term analyses available and provides important insights into the efficacy of this material in clinical practice.

METHODS

Data were collected from patients who underwent CP between December 2001 and December 2008. We conducted a retrospective study of a case series of 101 adult and pediatric patients who received custom-made HA implants after craniotomy for various reasons. The study was conducted in 2 hospitals: Santa Maria della Misericordia Hospital in Udine and Cannizzaro Hospital in Catania.

Customized cranial prostheses were designed using a standard reverse engineering process. On the basis of detailed CT scan data of the patient's skull, the prostheses were designed and manufactured by Fin-Ceramica Faenza S.p.A. according to the surgeon's specifications and delivered to the neurosurgical center in 2 copies—1 as the primary prosthesis and 1 as a backup.

The primary endpoint was to evaluate prosthesis survival and explantation rates. Secondary endpoints included the incidence of adverse events and the rate of surgical revision. Exclusion criteria were follow-up of <6 months, reconstruction with materials other than HA and multiple procedures. Data were collected and stored anonymously.

As this was an observational study of an established surgical practice, ethical approval was not required. A comparison with the existing literature was performed to compare our results with previously reported results and to assess differences between different materials.

Data were collected and organized using Microsoft Excel, which was also used to create tables and graphs. Statistical analysis was performed using IBM SPSS Statistics, version 28.0.0.0 (190). The Kaplan-Meier method was used to analyze survival rates, and the LIFETEST procedure was used to evaluate time-to-event data, providing detailed insights into the long-term outcomes of HA CP.

RESULTS

Over a period of 7 years (from December 2001 to December 2018), a total of 101 patients who underwent CP with custom-made HA prostheses at 2 different hospitals were included in this study. Of these, 51 patients were treated at the Santa Maria della Misericordia Hospital in Udine and 50 patients were treated at the Cannizzaro Hospital in Catania.

The study cohort consisted of 33 women and 68 men with a mean age of 41.3 years (range: 14–76 y; median: 40 y).

Supplemental Table 1, Supplemental Digital Content 1, http://links.lww.com/SCS/H309.

Craniotomies were performed for the following indications:

- Decompressive craniotomy (DC): this procedure was performed in 53 patients. Of these, 44 patients (mean age 37.2 y) underwent decompression for intracranial hypertension due to trauma and 9 patients (mean age 42.6 y) for vascular causes such as intracranial hemorrhage or ischemic stroke.
- Demolition craniotomy: this was performed in 26 patients for the surgical treatment of tumors. Specifically, 25 patients had bone tumors and 1 patient had a brain tumor, with an average age of 52.5 years.
- Post-traumatic craniotomy: this procedure was required in 7 patients with comminuted fractures, with an average age of 34 years.
- Secondary craniotomy: this was performed in 15 patients due to complications from previous surgery. Of these, 10 patients (mean age 28.4 y) underwent craniotomy for problems related to autologous bone resorption or infection, and 5 patients (mean age 42.4 y) underwent secondary craniotomy due to failure of the custom bone prosthesis, such as rejection.

The majority of DC were performed using the standard frontotemporoparietal flap, which was the most common approach, occurring in 40 patients (39.9%). Both the standard bifrontal craniectomy and the standard occipital flap were relatively rare, each performed in only 2 patients (2%). Less commonly, DC was performed in alternative locations, including the temporoparietal, parietal, or frontal regions, which together accounted for 40 patients (39.9%).

Skull reconstruction with CP was performed immediately in 22 cases. The mean interval between craniotomy and CP was 456 days (14.6 mo), with a range of 0 to 7991 days and a median of 241 days.

All patients were initially evaluated 30 days after CP, with subsequent follow-ups at 6 months, 12 months, 24 months, and then at 3, 4, 5, 10, and 15 years. Data availability at each follow-up point was as follows: 100% at 30 days, 96.04% at 6 and 12 months, 91.09% at 24 months, 80.20% at 3 years, 71.29% at 4 years, 59.41% at 5 years, 46.53% at 10 years, and 40.59% at 15 years.

There were 5 deaths in the study cohort, all occurring at least 10 years after CP. Of the patients included in the study, 46 were lost to follow-up. However, all of these patients were followed for at least 1 year after CP.

We distinguished between major and minor complications, with major complications defined as those leading to explantation of the HA prosthesis. Following such complications, patients were excluded from further follow-up in the study. Major complications were observed in 9 patients: 3 at the Santa Maria della Misericordia Hospital in Udine (5.9% of patients treated there) and 6 at the Cannizzaro Hospital in Catania (12% of patients treated there). The reasons for explantation were as follows:

- Three cases of infection.
- Two cases of tumor recurrence.
- Two cases of fracture.
- One case of cicatrial retraction.
- One case of cerebral hemorrhage.

In all cases, the complications appeared to be related to the surgical procedure rather than the device used in CP. The mean time from CP to major complication was 38 months (range:

0–107 mo), with a median of 33 months. Of the patients who required prosthesis explantation due to complications, 4 received the HA backup CP and 1 patient received a prosthesis made from a different material. Of those requiring explantation, 3 were second-line patients due to custom bone prosthesis failure, representing 33.3% of the major complication population and 4.95% of the general population.

Minor complications occurred in 10 cases (10% of patients): 3 in Udine and 7 in Catania. These included:

- Three cases of fracture.
- Two cases of tumor recurrence.
- One cases of infection.
- One case of cicatrizial retraction.
- One case of mobilization.
- One case of epilepsy.
- One case of hydrocephalus.

All minor complications were resolved without the need for explantation of the HA prosthesis.

At the 15-year follow-up, radiographic and clinical evaluations of 41 patients confirmed optimal results, with complete and stable integration of the implant into the surrounding bone and no significant resorption or migration (Figure 1; Supplemental Table 2, Supplemental Digital Content 1, http://links.lww.com/SCS/H309).

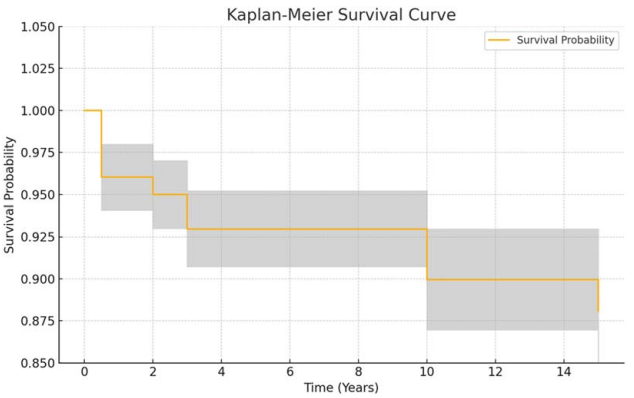

FIGURE 1. Kaplan-Meier survival curve showing the probability of survival over 15 years for patients who underwent cranioplasty with custom-made HA prostheses. The curve starts at 100% and falls to ~88% at 15 years, indicating good long-term outcomes.

DISCUSSION

Cranioplasty remains a critical procedure in neurosurgery, with the choice of material playing a key role in long-term outcomes. While previous research has investigated various materials such as titanium, PMMA, PEEK, and autogenous bone, gaps remain in understanding the long-term performance of HA implants. Among synthetic bone substitutes, hydroxyapatite is a well-established material for cranioplasty; it is biocompatible, mimics the mineral structure of bone, does not cause foreign body reactions and has good osteointegration properties. Recent literature even suggests that HA has the lowest risk of infection among heterologous materials.[10–14] However, despite these advantages, HA also has its disadvantages. Before full bone integration, HA is brittle and prone to fracture or dislocation, raising concerns about its durability over long follow-up periods.[15,16]

The fragility of customized PHA cranioplasty implants increases if the surgeon fails to achieve accurate design and validation and/or accurate surgical procedures.

A mathematical model showed that when local and general discontinuities of the cranioplasty with the bone perimeter were included in the test scenarios, the load on the cranioplasty implant increased by 80% and 50%, respectively. This increases the risk of cranioplasty fracture.[17]

Careful attention during these phases helps to maintain the resistance of the implant under the most favorable mechanical conditions, without compromising its biomimetic capacity.

This highlights the need for further research into the long-term performance and complications associated with HA implants.

Osteointegration is a key feature that has been extensively studied in the literature.[1] Previous studies have reported effective integration rates ranging from just under half (49.8%) in the first 6 months after surgery to 74.5% at later evaluations.[9,14,18] Staffa et al[19] reported that in a series of 60 patients with porous hydroxyapatite (PHA) cranioplasty, good integration was observed in most cases, with only 11.7% showing suboptimal integration (<75%). In addition, the systematic review by Morselli and colleagues showed that patients with PHA implants had a lower rate of postoperative infection and explantation than patients with other materials such as PMMA, PEEK, and titanium. However, the rate of prosthesis migration was significantly higher, probably due to the fragility of the HA implant.[20]

Our study, one of the most comprehensive to date, provides valuable insight into the long-term performance of custom hydroxyapatite cranioplasty. With a cohort of 101 patients followed for up to 15 years, we observed a prosthesis survival rate that underscores the efficacy of the material. Major complications requiring prosthesis explantation occurred in 9 patients, while minor complications were observed in 10 cases. Importantly, radiographic and clinical evaluations at 15 years showed stable integration of the HA implants in 41 patients, with no significant resorption or migration.

The multicenter European study by Zaed and colleagues, which included 494 patients treated with PHA cranioplasty, reported a complication rate of 7.9% and an explantation rate of 4.3%. Fractures and prosthesis dislocation were most common in the early phase of implantation, before complete osteointegration. This finding is consistent with the inherent fragility of HA implants, which is most pronounced in the early postoperative period and during the process of osseointegration, when the mechanical strength of the implant can decrease by 15% to 30%.[8]

Moles et al[21] conducted a long-term comparative study between HA and autogenous bone cranioplasty in 100 patients. They found no significant difference in complication rates between the 2 groups. However, fractures were a notable problem in the HA group, occurring in 20.8% of cases. They concluded that although custom-made HA prostheses offer cosmetic advantages, their porous structure makes them fragile in the short-term and the effectiveness of long-term osseointegration remains uncertain. Notably, the follow-up period in their study was significantly shorter than in our analysis, where patients were followed for up to 15 years.

Our study is not without its limitations. The retrospective nature of the analysis and the lack of a control group using alternative materials limit our ability to draw definitive conclusions about the superiority of hydroxyapatite. In addition, the loss of 46 patients to follow-up may introduce bias, although all patients were followed for at least 1 year. Future studies should aim to include larger cohorts with prospective designs and comparative analyses of different materials.

The promising results observed in this study suggest that HA is a viable option for long-term cranial reconstruction. Future research should focus on refining surgical techniques to further reduce complication rates and exploring the use of adjunctive therapies to improve implant integration. In addition, comparative studies with other materials, particularly in randomized controlled trials, would provide more robust data on the relative advantages and disadvantages of HA in cranioplasty. The inherent fragility of HA can be mitigated by precise planning and careful intraoperative handling, which, as demonstrated in our study, can significantly reduce the risk of fracture and displacement. The primary fragility of the HA implant is expected to resolve within 3 months to 1 year, as the prosthesis acquires mechanical resistance through progressive osseointegration.

CONCLUSION

This study provides a comprehensive long-term evaluation of custom HA CP, providing valuable insight into its efficacy and safety over a 15-year follow-up period. Our findings support the viability of HA as a material for cranial reconstruction, demonstrating a high prosthesis survival rate with stable integration in the majority of patients. The complications observed, including fractures and infections, were consistent with the literature, particularly in the early postoperative period and during the osseointegration phase. Importantly, the results suggest that the fragility of HA implants can be effectively managed through careful surgical planning and handling, contributing to the long-term success of the procedure.

REFERENCES

1. Zaed I, Cardia A, Stefini R. From Reparative Surgery to Regenerative Surgery: State of the Art of Porous Hydroxyapatite in Cranioplasty. *Int J Mol Sci* 2022;23:5434
2. Agrawal M, Mishra K. Neurocognitive outcome post cranioplasty: the role of cerebral hemodynamics and cerebrospinal fluid dynamics. *Surg Neurol Int* 2024;15:204. https://doi.org/10.25259/SNI_1003_2023
3. Shah A, Jung H, Skirboll S. Materials used in cranioplasty: a history and analysis. *Neurosurg Focus* 2014;36:E19. https://doi.org/10.3171/2014.2.FOCUS13561
4. Zanotti B, Zingaretti N, Verlicchi A, et al. Cranioplasty: review of materials. *J Craniofac Surg* 2016;27:2061–2072
5. Sprio S, Fricia M, Maddalena GF, et al. Osteointegration in cranial bone reconstruction: a goal to achieve. *J Appl Biomater Funct Mater* 2016;14:470–476
6. Martini L, Staffa G, Giavaresi G, et al. Long-term results following cranial hydroxyapatite prosthesis implantation in a large skull defect model. *Plast Reconstr Surg* 2012;129:625–535
7. Fricia M, Passanisi M, Salamanna F, et al. Osteointegration in custom-made porous hydroxyapatite cranial implants: from reconstructive surgery to regenerative medicine. *World Neurosurg* 2015;84:591.11–591.16
8. Zaed I, Rossini Z, Faedo F, et al. Long-term follow-up of custom-made porous hydroxyapatite cranioplasty in adult patients: a multicenter European study. Can we trust self-reported complications? *J Neurosurg Sci* 2022;66:335–341
9. Fricia M, Nicolosi F, Ganau M, et al. Cranioplasty with porous hydroxyapatite custom-made bone flap: results from a multicenter study enrolling 149 patients over 15 years. *World Neurosurg* 2019;121:160–165
10. Bruno Z, Angelo N, Riccardo S, et al. Custom-made hydroxyapatite cranioplasty: radiological and histological evidence of bone-biomaterial osteointegration in five patients. *Asian J Neurosurg* 2020;15:198–203
11. Ono H, Sase T, Tanaka Y, et al. Histological assessment of porous custom-made hydroxyapatite implants 6 months and 2.5 years after cranioplasty. *Surg Neurol Int* 2017;8:8. https://doi.org/10.4103/2152-7806.198735
12. Okii N, Nishimura S, Kurisu K, et al. In vivo histological changes occurring in hydroxyapatite cranial reconstruction—case report. *Neurol Med Chir* 2001;41:100–104
13. Messina G, Dones I, Nataloni A, et al. Histologically demonstrated skull bone integration in a hydroxyapatite prosthesis in a human. *Acta Neurochir (Wien)* 2011;153:1717–1718
14. Maenhoudt W, Hallaert G, Kalala JP, et al. Hydroxyapatite cranioplasty: a retrospective evaluation of osteointegration in 17 cases. *Acta Neurochir (Wien)* 2018;160:2117–2124
15. Spennato P, Hallaert W, Kalala G, et al. Hydroxyapatite ceramic implants for cranioplasty in children: a retrospective evaluation of clinical outcome and osteointegration. *Childs Nerv Syst* 2020;36:551–558
16. Frassanito P, De Bonis P, Mattogno PP, et al. The fate of a macroporous hydroxyapatite cranioplasty four years after implantation: macroscopical and microscopical findings in a case of recurrent atypical meningioma. *Clin Neurol Neurosurg* 2013;115:1496–1498
17. Zanotti B, Verlicchi A, Indiani S, et al. Spontaneous fractures in custom-made porous hydroxyapatite cranioplasty implants: is fragility the only culprit? *Acta Neurochir (Wien)* 2015;157:517–523
18. Briel J, Chartier T, Chaput C, et al. A new custom made bioceramic implant for the repair of large and complex craniofacial bone defect. *J Craniomaxillofac Surg* 2013;41:403–407
19. Staffa G, Barbanera A, Faiola A, et al. Custom made bioceramic implants in complex and large cranial reconstruction: a two-year follow-up. *J Craniomaxillofac Surg* 2013;40:65–70
20. Morselli C, Zaed I, Tropeano MP, et al. Comparison between the different types of heterologous materials used in cranioplasty: a systematic review of the literature. *J Neurosurg Sci* 2019;63:723–736
21. Moles A, Heudes PM, Amelot A, et al. Long-term follow-up comparative study of hydroxyapatite and autologous cranioplasties: complications, cosmetic results, osseointegration. *World Neurosurg* 2017;111:395–402