



Patient-specific titanium-reinforced calcium-phosphate (CaP: Ti) implants for revision cranioplasty

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ABSTRACT

Introduction: Cranioplasty is a common neurosurgical procedure, but infections can complicate it, necessitating revision surgery. Alloplastic patient-specific implants (PSI) are increasingly utilized, and different materials are available. This study evaluates the role of titanium-reinforced calcium-phosphate (CaP:Ti) implants in revision cranioplasty.

Research question: Assessing the efficacy and safety of CaP:Ti PSI in patients requiring revision cranioplasty following complications with previously failed cranioplasty attempts.

Material and methods: Retrospective analysis of 15 patients who underwent CaP:Ti PSI implantation for revision cranioplasty between 2016 and 2022 at a single neurosurgical department. Data on demographics, perioperative details, and outcomes were collected and assessed. Differences in distribution were assessed using Fisher's exact test, and groups were numerically compared using student's t-test. A p-value <0.05 was considered statistically significant.

Results: In most patients, CP failure occurred early (38 days) following elective craniotomy for tumor and vascular procedures. The first revision cranioplasty was conducted in 12 cases using CaP:Ti PSI in 8 cases successfully requiring no further revision. Three cases implanted with other alloplastic materials required revision and received CaP:Ti PSI in the second (n = 2) or third (n = 1) CP attempt. The overall success rate for CaP:Ti PSI was 73.3% over more than two years of follow-up. success rate in revision cranioplasty. Surgical site complications, predominantly infections, were the main cause of CP failure. The average interval between implant removal and re-cranioplasty was 300 days. Prehabilitation using skin expanders and postoperative antibiotic use were strategies successfully utilized in this cohort.

Discussion and conclusion: Our findings suggest that CaP:Ti PSI implants hold promise in salvaging complicated cranioplasty in most cases despite challenges such as infection and implant failure. The use of techniques like skin expanders may contribute to better outcomes. However, further research is crucial to establish optimal timing and patient selection guidelines in revision cranioplasty using CaP:Ti implants, which could significantly impact future neurosurgical practices.

1. Introduction

The rate of surgical site infection (SSI) after craniotomy (CO) has been reported to be between 1 and 15% (Jiménez-Martínez et al., 2019;

Korinek, 1997; Korinek et al., 2006; McClelland and Hall, 2007; Raggueneau et al., 1983). Most SSIs are superficial and do not require bone flap removal (BFR) (Bruce and Bruce, 2003); however, in cases of infection affecting the bone autograft, BFR may become necessary.

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Similarly, patients who require a decompressive craniectomy and subsequent CP reportedly have high rates of reoperation and BFR or explantation of the implant (Giese et al., 2021; Sauvigny et al., 2021).

Replacement of the explanted BF (repeat CP) is typically conducted using alloplastic materials, such as plastics, ceramics, or metal (Alkhaibary et al., 2020; Siracusa et al., 2021), and can either be conducted immediately following BFR within the same surgical session or as staged procedure (G et al., 2023). While the earliest cranioplasties may have been conducted in pre-columbian Peru more than 4000 years ago using e.g. metal plates, neurosurgeons in the 20th century treating head-injured patients in the aftermath of industrialized warfare utilized improvements in material sciences of their time to develop novel implants and surgical techniques for CP (Shah et al., 2014; EL, 1941). While studies examining the role of alloplastic materials in repeat CP are sparse, alloplastic materials have been extensively studied in primary CP following decompressive craniectomy (DC), especially as the traditionally utilized autologous bone fragment is more and more scrutinized (Giese et al., 2020, 2021; Sauvigny et al., 2021; van de Vijfeijken et al., 2018; Vince et al., 2019; Yuruk et al., 2023).

Alloplastic materials can generally be subdivided into 3D-formed (printed or machined) patient-specific implants (PSI) and intraoperatively crafted implants formed, e.g., from a sheet of titanium mesh or bone cement.

The first 3D-designed CAD/CAM machined implants were tested over twenty years ago and initially manufactured from polymethyl methacrylate (PMMA), titanium, or carbon fiber (Saringer et al., 2002). These materials typically do not integrate into the skull and remain a “foreign body”, potentially susceptible to later infection (Conen et al., 2020). Advances in material science in recent years addressed this issue by developing several implants potentially capable of ossification, spanning from bioactive glass compounds to hydroxyl-apatite, a subtype of calcium-phosphate (CaP) (Piitulainen et al., 2019; Posti et al., 2016; Stefini et al., 2015). The latter is, partly due to its microporous structure, perceived to especially facilitate ossification and natural integration of the implant into the skull (Zaed et al., 2022). However, the fragility of this material remains problematic, especially when considering younger patients with good neurological outcomes whose physical activity may place them in jeopardy for skull trauma and potential implant fracture.

Reinforcing the ceramic structure with a titanium scaffold was proposed to remedy this problem by significantly increasing the compound material's tensile and impact strength over pure titanium or Ca-P components (Omar et al., 2020). Clinical evaluation of this implant (formerly manufactured by OssDsign AB, Sweden) revealed its widespread applicability to naïve cranioplasty patients with low complication rates and suggested successful osseous integration (Wesp et al., 2022).

Few studies thus far systematically examined the use of PSI in repeat-CP cases using biologically inert materials (Giese et al., 2020; Koper et al., 2019; Potter et al., 2023). Additionally, the use role topical and postoperative antibiotic treatment as well as the ideal timing for repeat-CP following BFR are still unclear. We thus aimed to report our experience with the bioactive CaP-Ti PSI in these complicated cases and present data on their perioperative management from our academic center.

2. Methods

We retrospectively reviewed the patient records of our neurosurgical department between January 2016 and December 2022 and identified all patients with the specific surgical code for CaP-Ti CP ($n = 38$). We then excluded patients who received a primary CaP-Ti implant for osseous tumor resection ($n = 6$), and those who received CaP-Ti CP following decompressive craniectomy without previous CP ($n = 17$) (see also Supplemental Table S1). For the remaining patients with a CaP-Ti implant for revision CP, data on the perioperative course, such as risk factors, comorbidities, intraoperative details, and patient demographic

data were collected and are presented descriptively. Moreover, differences in distributions were assessed using Fisher's exact test, and groups were compared using student's t-test. A p-value <0.05 was considered statistically significant. Statistical analysis and figure design were performed with Prism 10 (GraphPad Software, Boston, MA, USA), the Medical Imaging Interaction Toolkit (V2023.12) (Wolf et al., 2005) and Adobe Illustrator (Adobe Inc., San Jose, CA, USA).

3. Results

We identified 15 patients (6M/9 F, Fig. 1 A) implanted with a Ca-P PSI for revision CP from 2016 to 2022. The mean follow-up after Ca-P CP was 764 ± 197 days. The initial cranial operations (CO) were predominantly elective tumor excisions ($n = 9$, 60%), but vascular operations ($n = 2$; 13.3%), trauma cases ($n = 2$; 13.3%) and one intracerebral abscess (6.67%) were also present. In one of the vascular operations, an elective excision of an arteriovenous malformation (Spetzler Martin grade 2) (Spetzler and Martin, 1986) was performed; the other case was a ruptured anterior communicating artery aneurysm with an associated subarachnoid hemorrhage (SAH) WFNS² (Teasdale et al., 1988). The two trauma surgeries were performed for dislocated skull fractures that were directly reconstructed using titanium screws and plates. The intracerebral abscess was spontaneous and related to a *Streptococcus intermedius* infection. In our collective, only one patient was included following DC for ischemic infarction. In all but this case (Patient 14), the autologous bone fragment was reimplanted during the initial operation. In the DC case, the autologous fragment was reimplanted alio loco several months following the bone fragment removal, which was thus counted as the initial CO. All repeat-CP procedures were conducted staged, i.e. not in the same surgical session as the BFR.

3.1. Initial craniotomy

The initial COs took place between 1991 and 2019, whereby 12 (80%) were conducted at our center and three (20%) at other hospitals. The craniotomy size was, on average, 29.7 ± 16 cm². During the initial surgery, six patients required dural reconstruction, which was conducted in four cases using autologous galea and in two cases using artificial dural replacement materials. In two cases, gelatin sponges were applied, and in one case, additional fibrinogen-matrix (TachoSil, Takeda Pharmaceuticals, Tokyo, Japan). Further intraoperative details are given in Table 2 and Fig. 2. In the case of the ischemic DC, the autologous bone flap was reimplanted 462 days following DC.

The median duration until the first complication was noted was 38 days after the initial CO and eventually led to the explantation of the autologous BF. Reasons for explanting the autologous BF were mostly infections ($n = 13$), although one CSF fistula and epidural hematoma were noted each as well.

3.2. Initial revision cranioplasty

The first alloplastic cranioplasty (re-CP1) was performed in 13 cases (86.67%) at our hospital. Two patients (13.33%) were operated elsewhere. In 12 cases (80%), re-CP1 was conducted using a Ca-P PSI. In three cases (20%), re-CP1 was performed using a material other than Ca-P. Of those, a PEEK implant was utilized in one case. In the other two cases, the material could not be ascertained due to those surgeries having been conducted alio loco. In four cases, a skin expander was utilized prior to re-CP1. On average, re-CP1 was conducted 300.5 ± 145 days after explantation of the autologous bone.

Twelve patients (80%) were administered antibiotics postoperatively (10 cephalosporins, 1 ampicillin, 1 meropenem). Patients were on average discharged on the sixth postoperative day (5.5 ± 2.9 d). The further course of eight patients (all CaP-Ti) was uneventful, and no adverse events were detected. One patient developed focal epilepsy on the 15th postoperative day, but was pharmacologically treated with

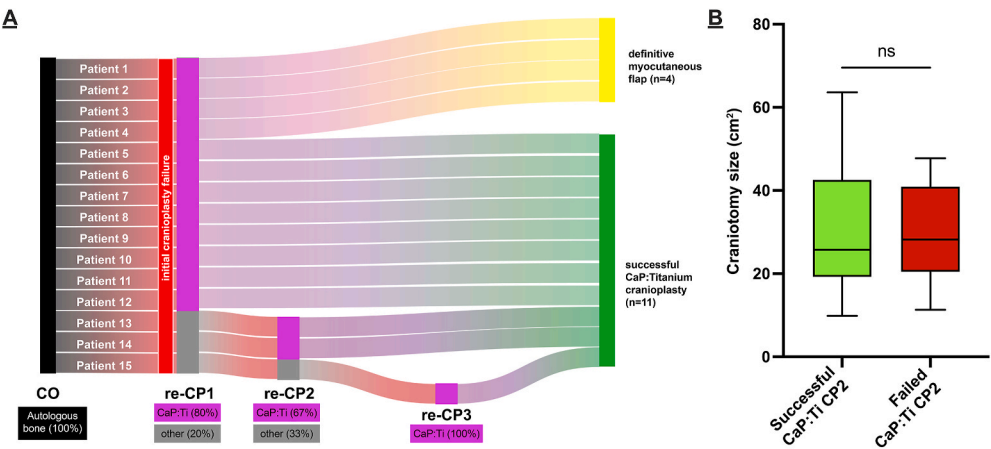


Fig. 1. Patient overview. **A:** Sankey chart illustrating the number of CP operations **B:** No significant difference was detected regarding the craniotomy size in patients with successful CaP:Ti CP or failed CP and definitive myocutaneous flap treatment ($p = 0.94$, unpaired t -test).

Table 1
Prevalence of commonly named risk-factors for CP failure in the study collective.

	Nicotine	Diabetes	Drug use (i.v.)	Hypertonus	CV	Renal insufficiency	Liver cirrhosis	Anticoagulation	Obesity	Immunosuppression
n (%)	8 (53.3%)	2 (13.3%)	1 (6.7%)	7 (46.7%)	4 (26.7%)	1 (6.7%)	2 (13.3%)	1 (6.7%)	3 (20%)	0 (0%)

Table 2
Operative and perioperative details.

	CO	Re-CP1	Re-CP2
Use of skin expander before surgery	none	26% (4/15)	33 % (1/3)
Duration (min)	307 ± 198	82 ± 39	121 ± 16
Postoperative antibiosis (duration)	7% (21d)	80% (6.1 ± 1.5d)	100% (6 ± 1.4d)

Perioperative data and operative time are shown for the initial craniotomy with cranioplasty (CO, $n = 12$), the first revision cranioplasty (re-CP1, $n = 15$) and the second revision cranioplasty (re-CP2, $n = 3$). Data were partially unavailable for patients not operated at our center.

success.

Six patients (40%), four of whom had been treated with CaP:Ti PSI, developed surgical site complications, on average 5.27 ± 9.34 years following re-CP1. Of note, in patients implanted with CaP:Ti PSI, surgical site complications were detected significantly earlier compared to non-CaP:Ti PSI (103.5 ± 65.11 days vs. 556.8 ± 433.8 days, $p = 0.0438$, unpaired t -test). In three cases (1 CaP:Ti, 1 PEEK, 1 unknown material), radiological findings suggested intracranial affection warranting immediate explantation of re-CP1. In the other three cases (all CaP:Ti), in the absence of radiological deep tissue infection, conservative wound treatment was attempted but failed in all cases, leading to explantation of re-CP1 on average 388 ± 349 days following the first detection of the surgical site complication. In these cases, definitive myocutaneous flaps were utilized, and skin closure could be achieved with satisfactory cosmetic results. Neither the prevalence of the risk factors named in Table 1 nor the size of the craniotomy were significantly different in patients with failed re-CP1 ($p > 0.5$ in all respective comparisons).

3.3. Further revision cranioplasties

In two patients with failed re-CP1, a third cranioplasty attempt (re-CP2) was undertaken 198.5 ± 46 days following the explantation of the cranioplasty material. Both patients received antibiotics intravenously for seven days postoperatively. One patient developed another superficial wound infection that was successfully treated without another

operation. No further complications were noted in these patients.

One female patient (Patient 15) presented to our center after microsurgical clipping of a ruptured MCA aneurysm, which had been treated elsewhere. After the failure of the autologous cranioplasty, two futile alloplastic cranioplasty attempts (re-CP1 and re-CP2) had been conducted at the previous hospital. When she presented twelve months following the last explantation, we conducted re-CP3 using a CaP:Ti implant in an 80-min surgical session. She received postoperative intravenous antibiotics for seven days. The patient recovered fully and reported a favorable cosmetic outcome.

4. Discussion

In this study we present data on 15 patients operated at our academic center for revision cranioplasty using a CaP:Ti compound implant. In all but four cases, revision cranioplasty using this material was successful in restoring the skull integrity. Virtually all alloplastic materials available for primary alloplastic CP are also utilized in revision CP. Similar to primary CP there is no clear consensus on the optimal material choice in these cases. There is evidence linking the CaP:Ti PSI with reduced postoperative infections compared to PMMA implants (Wesp et al., 2022), and the potential for de novo bone growth of this material has been demonstrated in vivo and ex vivo (Omar et al., 2020; Sundblom et al., 2021), making it especially interesting in cases of revision CP. At our center, it was exclusively used in the study period for revision CP. In absence of another CP material, the innate material-specific properties therefore cannot be examined in direct comparison with other materials, but aspects of surgical technique are discussed in the following section.

4.1. Immediate vs. staged revision cranioplasty

In cases of revision surgery, a multitude of strategies have been successfully employed, either in form of immediate cranioplasty within the same surgical session or by employing a staged procedure (Bruce and Bruce, 2003; Conen et al., 2020).

The former includes strategies of topical antibiotic treatment of the bone flap followed by reimplantation, implantation of a constant antibiotic irrigation system enabling postoperative topical antibiotic treatment, or the removal and replacement of the bone flap with a sterilized

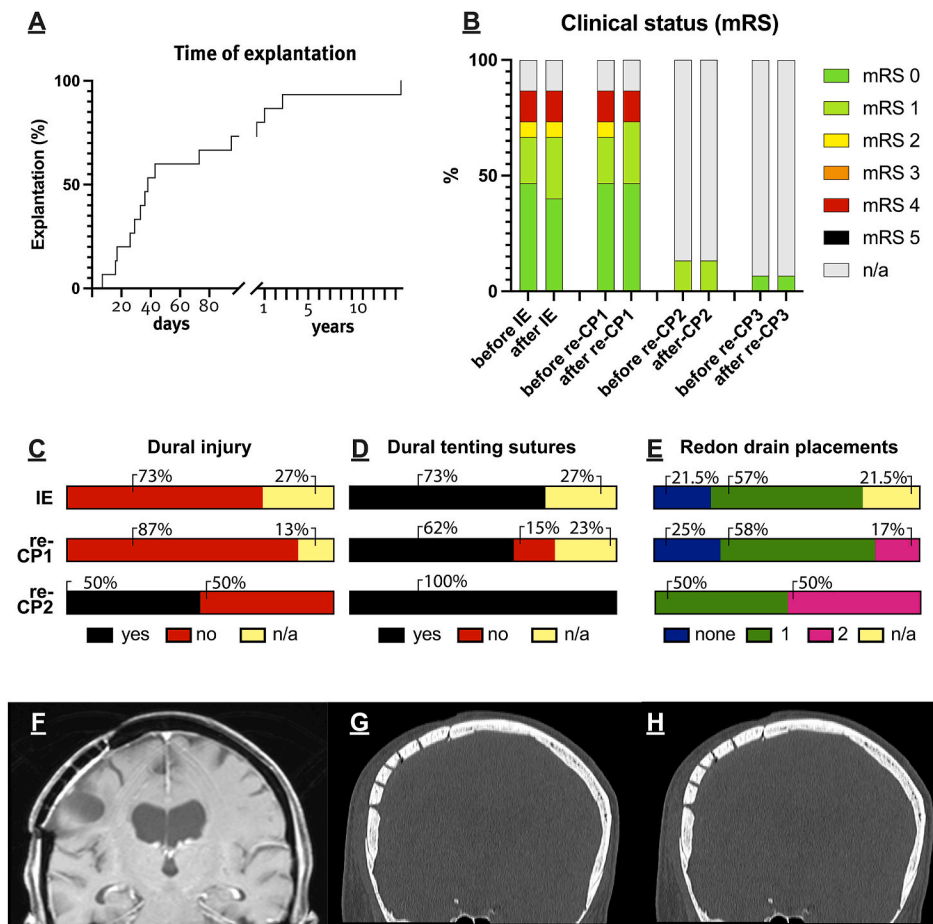


Fig. 2. Intra- and perioperative details of patients undergoing repeat-CP. **A:** Most CP-explantations occurred within the first 100 days following CP, with the marked exception of one case presenting more than ten years following the initial CP. **B:** Clinical status remained similar before and after CO, re-CP1 and re-CP2 (Fisher's exact test >0.5 in all cases). **C-E:** Neither inadvertent dural injury, dural tenting sutures or subgaleal redon drain placement were significantly different between surgical interventions (Fisher's exact test >0.5 in all cases). **F:** MRI of a patient with infection of an alloplastic implant (failed re-CP1). **G:** The implant was removed and the skin allowed to heal before the CaP:Ti implant was placed. **H:** Postoperative CT scan showing restored cranial integrity after CaP:Ti re-CP2.

titanium mesh (Conen et al., 2020; Auguste and McDermott, 2006). The main upside of the single-staged procedure lies in avoiding a secondary surgery after wound healing when increased scarring can significantly complicate a revision CP (Conen et al., 2020). However, while topical antibiotics can prove successful, immediate reimplantation of the bone flap harbors residual risk of remnant sources of infection, and the immediate implantation of alloplastic materials such as titanium meshes into an infection-ridden microenvironment is associated with a significant risk for recurrent complications (Kubota et al., 2021; Mukherjee et al., 2014).

Staged surgery, that is removal of the bone flap followed by intra-venous and, if indicated, prolonged oral antibiosis and close observation of wound healing before attempting a secondary cranioplasty is the second possible approach for these patients (Conen et al., 2020; Koper et al., 2019; Potter et al., 2023). While this technique is founded on the idea of achieving the largest amount of primary debridement initially, progressive scarring can complicate further surgical interventions. Additionally, this approach necessitates patients to undergo a second surgery with both, an accompanying risk to them and additional costs to the respective health system (Conen et al., 2020; Koper et al., 2019).

To date, no strategy has definitely been proven superior, and while guidelines have been proposed, the decision which treatment route is taken lies with the operating surgeons and their institutional guidelines (Conen et al., 2020). In recent years, our department exclusively employed the latter, two-staged strategy. While initially, intra-operatively formed bone cement cranioplasties were used for re-CP, the

advent of CAD/CAM PSI enabled us to design and tailor the implants preoperatively, e.g. by reducing convexity to enable a tension-free skin adaptation. Titanium-reinforced CaP:Ti is a relatively novel material used for cranioplasty. In several studies, this material was proven a potent competitor to the ubiquitously used PMMA or PEEK cranioplasty materials in naïve CP following DC, but has thus far not been specifically investigated regarding revision cranioplasty (Wesp et al., 2022; Kihlström Burenstam Linder et al., 2019).

In this study, we aimed to elucidate the role, CaP:Ti implants can play in patients with previous surgical site complications warranting the explantation of the autologous bone flap. Surprisingly, we found a number of patients indeed not only presenting after failed autologous CP for revision, but several that underwent three or even four cranioplasty attempts until either the decision against another CP was made and definitive myocutaneous flap treatment initiated (Fig. 1A, top), or CP was conducted successfully (Fig. 1A, bottom). In total, the rate of successful CP was 73.3% in our collective, and 66.7% when considering only patients with one prior CP attempt (Fig. 1). In case of revision cranioplasty, varying success rates for PSI implantation have been reported in the literature, ranging from 90% using PEEK to 50%–95% using PMMA (Koper et al., 2019; Potter et al., 2023). However in light of the low number of patients these studies report from, these success rates should be regarded with caution (Koper et al., 2019; Potter et al., 2023). At first glance, the success rates reported here, and in the literature for staged PSI implantation are markedly lower than recently reported numbers for single-staged titanium mesh implants, where reoperation

rates ranged from 0 to 25% (Potter et al., 2023; Di Rienzo et al., 2021; Ehrlich et al., 2017; Kshetry et al., 2012; Wind et al., 2013; Yoshioka, 2018). It should, however, be noted that the largest amongst these series included a followed-up of less than one year after titanium mesh CP (Potter et al., 2023; Di Rienzo et al., 2021; Ehrlich et al., 2017; Kshetry et al., 2012; Wind et al., 2013; Yoshioka, 2018). This is especially problematic in light of the low long-term (four year) retention rate of 46.8% reported for titanium mesh implants in some patients (Kwiecien et al., 2018). Additionally, while the immediate advantages of titanium mesh are apparent, the 0.6 mm thick mesh implanted in these studies is significantly inferior regarding stability when compared with the CaP:Ti compound implant, calling the long-term viability of these implants for neurologically intact patients further into question (Omar et al., 2020; Murphy et al., 2016). Additionally, tension-free adjustment with just the right amount of curvature requires significant experience in handling to achieve a cosmetically satisfactory outcome. Contrary to pure titanium, the microporous structure of the implant used in our study additionally enables antibiotic loading of the implant (Sundblom et al., 2019). In light of the present discontinuation of the implant type used in our study by the manufacturer, titanium mesh implant remains a valid alternative for small defects with little putrid infection.

4.2. Timing of revision cranioplasty and prehabilitation

The optimal timing of revision cranioplasty after BFR is controversial and the decision must ultimately be made on an individual basis. In our collective, we performed the first revision cranioplasty on average 300 days, and in case of re-CP1 failure, the second revision 200 days following the removal of the previous implant. This is in line with previous studies, where an interval of 6–12 months is commonly reported (G et al., 2023; Koller et al., 2020).

Clear guidelines are difficult to establish due to the paucity of data from these patients and the high interindividual heterogeneity, owing to craniotomy size and incision location. Leaving patients without an implant is disfiguring and may expose the brain to potential trauma. Furthermore, changing CSF dynamics can adversely affect neurological rehabilitation. Additionally, in cases of sunken skin flaps, scar tissue may additionally impede a revision cranioplasty. Some authors therefore argue for as-early as possible revision cranioplasty after BFR for SSI, even before concluding antibiotic treatment to prevent tissue shrinkage due to scarring, a philosophy we do not follow. In these cases, where skin conditions are exceedingly difficult and a tension-free skin adaptation over the implant is foreseeably impossible, we found skin-expanders a potent tool (Lo et al., 2022). Their implantation is managed closely by our colleagues from the maxillofacial surgery department and the gradual filling of the device stimulates a significant gain in soft tissue, enabling tension-free adaptation. Taken together, in our experience, a revision cranioplasty should be conducted as early as possible, but only after completed wound healing and in an infection-free state. Usage of skin-expanders may additionally aid surgeons achieve favorable outcomes.

4.3. Intra- and perioperative considerations

The operative regiment for repeat-CP in our institutions follows commonly known guidelines and routine placement of dural tenting sutures and redon drains. The routine placement of dural tenting sutures in naïve craniotomies has been challenged, primarily due to the risk of inadvertent cortical injury (Kunert et al., 2021; Winston, 1999). In cases of revision CP, the dural tissue is often thickened and scarred, reducing the risk of inadvertent cortical injury. Further, although not systematically assessed by studies, placement of dural tenting sutures is commonly perceived to reduce the epidural space, reducing the risk of epidural fluid collections potentially conducive to implant infection (Krishnan and Maurya, 2024; Raju et al., 2023). Additionally, placing postoperative subgaleal drains, in our practice redon drains (Redon

et al., 1954), can further reduce the risk of potentially infection-cultivating fluid accumulation surrounding the implant, and has been repeatedly shown to positively affect surgical outcomes after naïve cranioplasty (Spake et al., 2021; Tong et al., 2015). In cases of CSF fistula, however, subgaleal drains can have potentially devastating complications and should be avoided or placed without suction (Scheer et al., 2023). The role of routine postoperative antibiotic treatment is controversial, especially in light of growing antibiotic resistance (Korinek et al., 2006; Menz et al., 2021; Mindermann, 2021). Our retrospective analysis revealed, that in the majority of revision CP cases, we used routine antibiotic treatment. This indeed reflects common practice in the literature, where colleagues reported to use prophylactic antibiotics even in naïve cranioplasty cases, however is not supported by high quality empirical evidence to date and should thus be cautiously practiced (Abode-Iyamah et al., 2018; Paredes et al., 2020).

4.4. Predictors of implant failure

Our study did not primarily aim to assess predictors of implant failure, which would necessitate analysis of the entire cohort of craniotomies performed in the observation period. However, a number of risk factors for CP failure have been reliably reported in the literature, chiefly, tobacco use and metabolic dysregulation (Sauvigny et al., 2021; Ernst et al., 2018; Rashidi et al., 2020; Di Rienzo et al., 2024; Korhonen et al., 2018). We assessed these factors in our collective (Table 1) and found that both tobacco use, as well as the prevalence of diabetes (a proxy for metabolic dysfunction), were markedly higher than reported for the general German population (Starker et al., 2022; Tamayo et al., 2016). It could well be that the repeated implant failure, e.g., seen in patients 13–15, is partially attributable to their tobacco use, which has been shown to adversely affect wound healing and implant survival.

In recent years, Cutibacteria (formerly known as Propionibacteria) and Staphylococci have also emerged as a relevant factor for osteolysis and CP failure requiring repeat CP (Dechaene et al., 2023; Kelly et al., 2006). In our retrospective study, we found a low rate of pathogen identification, with only Staphylococcus and no Cutibacteria identified. It can, though, not be ruled out that especially the futile conservative wound treatment observed after re-CP-1 is partially attributable to colonization with these pathogens. To date, no best practices for managing these patients have been defined, although hydroxyl-apatite implants, chemically closely related to the CaP implants in our study, have been suggested to show benefits in patients with latent infection (Dechaene et al., 2023; Millward et al., 2022; Iaccarino et al., 2018).

4.5. Limitations

Our study has several limitations, stemming primarily from its retrospective design and small study cohort. Due to the lack of a control group not undergoing implant failure, assessing risk factors was impossible. During the study period, CaP:Ti was the material of choice at our center for revision cranioplasty, making a direct comparison with other materials impossible. Further, as several previous CP surgeries were not conducted in-house, documentation of these procedures was not as closely available. A large limitation to the investigation of the further use of CaP:Ti implants is the manufacturer's current discontinuation of the product.

5. Conclusion

Our data suggest that Ca-P PSI could be a valuable asset for rescue cranioplasty in complicative cases. Over two-thirds of repeat CP patients could be definitely treated using the innovative material. Additional use of skin expanders may be helpful to surgeons in revision cranioplasty cases. Due to the small study population, further, ideally, multicenter studies are warranted to elucidate the mechanism and develop guidelines for repeat CP.

Ethics approval

This retrospective chart review study involving human participants was in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Due to the retrospective character of the investigation, the Human Investigation Committee (IRB) of Heidelberg University was consulted and waived informed patient consent.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.bas.2025.104213>.

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