Clinical relevance of current materials for cranial implants
Towards an optimal patient-specific implant material
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CHAPTER 10

General discussion and future perspectives
GENERAL DISCUSSION AND FUTURE PERSPECTIVES

The objective of this thesis was to identify and to fill gaps in the current understanding of techniques and materials for cranioplasties by analyzing the available evidence and systematically collecting and evaluating data. We made a step forward towards the prerequisites and development of a new material for cranioplasties. Despite the new findings in this thesis, our research has not yet standardized the management of cranioplasties. Literature research was often restricted by studies with small patient samples, the inability to carry out a study that would offer convincing evidence, and the limited amount of currently available evidence regarding cranioplasties. This hinders clinical practice, but also complicates the design and execution of methodologically sound studies on cranioplasties. In this chapter, we reflect on our research findings and offer some possibilities for future developments, in which several challenges must be overcome.

Lack of definitions, protocols and guidelines
One of the main findings in this thesis is that there is no standard treatment and no standardized or generally accepted protocol for decompressive craniectomy nor cranioplasty.

The available literature shows that the definition of complications, including infection and resorption, diverges widely\(^1,2\). Multiple factors need to be considered according to the nature of the cranial defect and the medical prognosis; systemic and local factors; size and form of the defect; goals of the reconstruction (protection and/or cosmesis), the choice of material and the manufacturing process.

One of the materials mostly used for cranioplasties is autologous bone. Autologous bone is associated with high resorption rates\(^3\). A commonly described definition for resorption discerns two types of resorption: thinning of the bone mass on imaging or by palpation (type I), and complete lysis of the inner and outer tabulae with loss of cerebral protection, requiring revision (type II)\(^2,4\). Most patients do not undergo a standardized follow-up CT-scan, unless the patient experiences symptoms, as pain, discomfort or cosmetic impairment. The lack of a standardized follow-up protocol including a CT-scan leads to underreporting of resorption rates. The resorption process differs among patients: some patients will not notice any resorption of the autologous bone at all and if a patient is asymptomatic, the need for a routine post-operative CT-scan in the follow-up is debatable.
On the other hand, a CT follow-up protocol for autologous bone might be considered for the follow-up of the bone integrity and surveillance of early signs of resorption and loss of the protective function of the reconstruction. If resorption is detected the patient may be encouraged to wear protection or an alloplastic cranioplasty might be considered.

**Materials for cranioplasties**

A wide range of materials for cranioplasty with different advantages and disadvantages exists (Table 1). No gold standard is available for the reconstruction material. The optimal reconstruction material may vary, depending on the patient characteristics and various clinical settings.

With the current evidence, autologous bone for cranial reconstructions may be abolished for various reasons, but mainly because of its high resorption rate. In chapter 3 we found a resorption rate of 9.1%. This number is based on the cranioplasties that were removed due to complaints of resorption (e.g. pain, cosmesis or a palpable defect). A prerequisite for autologous bone preservation is an adequate and regulated bone bank. The increased demands for quality control and the novel regulations for bone banks in hospitals hamper the application of autologous bone for cranial reconstructions in many institutes and countries. The increased expertise and evolution of 3D virtual planning software and additive manufacturing (CAD/CAM) techniques allows the surgeon to choose for alloplastic cranial implants as a good alternative. This is especially the case in economically developed countries. On the other hand, hospitals need the equipment and expertise in terms of 3D planning software, 3D printers or CAD/CAM machines. Apart from these factors, the surgical team needs experience with the implantation of alloplastic materials and enough financial resources should be available to design and manufacture an alloplastic cranioplasty. In countries where a virtual planned and printed cranioplasty is not an option, autologous bone may be the best option for reconstruction, at least in order to protect the brain initially. For this purpose the autologous bone should be stored in a freezer or in an abdominal pocket.

Most frequently used alloplastic materials for cranioplasties are PMMA, titanium, hydroxyapatite and PEEK. Each material has its own specific characteristics (Table 1).
Table 1. Characteristics of materials used for cranioplasties

<table>
<thead>
<tr>
<th></th>
<th>Autologous Bone</th>
<th>PMMA</th>
<th>Titanium</th>
<th>Hydroxyapatite</th>
<th>PEEK</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aesthetics</td>
<td>✗</td>
<td>✓</td>
<td>✓</td>
<td>✗</td>
<td>✓</td>
</tr>
<tr>
<td>Biocompatibility</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Costs</td>
<td>✓</td>
<td>✓</td>
<td>✗</td>
<td>✓</td>
<td>✗</td>
</tr>
<tr>
<td>Exothermic reaction</td>
<td>✓</td>
<td>✗</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Intra-operative adjustments</td>
<td>✓</td>
<td>✓</td>
<td>✗</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Regenerates into bone</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
<td>✓</td>
<td>✗</td>
</tr>
<tr>
<td>Resterilization</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
<td>✓</td>
</tr>
<tr>
<td>Safe for the surgeon</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Thermal conduction</td>
<td>✓</td>
<td>✓</td>
<td>✗</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Thermal stability</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
<td>✓</td>
</tr>
<tr>
<td>Toxicity</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Possible to manufacture 3D PSI</td>
<td>✗</td>
<td>✓</td>
<td>✓</td>
<td>✗</td>
<td>✓</td>
</tr>
</tbody>
</table>

✓: Successful results provided in earlier studies
✗: Negative results provided in earlier studies
Ø: No consensus in literature, further research is required
The various materials differ substantially as to their suitability. Many different types of PMMA or PMMA-based materials are available in the medical field. PMMA is a reconstructive polymer, which is formed through the polymerization of PMMA particles with a liquid MMA. This conversion is never complete and residual monomers will remain in the implant. These residual monomers may cause toxic reactions and it is not possible to 3D print PMMA yet. PMMA does not have the properties for bony ingrowth, and therefore no commensurately growth with the cranium will follow. PMMA is relatively cheap, easy to use and radiolucent.

Not all hospitals have the opportunity to use computer software for designing and manufacturing a cranioplasty. But some surgeons do use molds for example of nylon, plaster, or silicon - (virtually designed or not) to improve the esthetic outcome of PMMA cranioplasties. In those cases there are a number of options to mechanically improve the cranioplasty. As shown in chapter 4 the manufacturing of PMMA cranioplasties under pressure ensures reduced porosity in the material. The results of chapter 4 lead to the advice to manufacture all PMMA cranioplasties preoperatively, in a safe environment under pressure of at least 2.2 bar to increase the mechanical properties. There are more benefits to manufacturing the cranioplasty preoperatively. One important advantage is that the cranial implant can be virtually designed using 3D planning software. Based on such a 3D planning, the implant can be manufactured using computer-aided manufacturing techniques. Another benefit could be that the polishing of the cranioplasty after manufacturing can be applied, resulting in a reduced biofilm and less bacterial adhesion. This may result in less re-operations due to a decreased number of infected cranioplasties. In our opinion, preoperative planning and manufacturing of the cranial implant leads to a more predictable surgical intervention and may result in a better fitting implants.

PEEK is used for Patient-Specific Implants (PSI) in adults. With the use of the patient's CT-scan and dedicated software it is possible to design a cranioplasty with an accuracy of at least 1 mm. In chapter 5 no significant prediction factor was found for the failure of PEEK cranioplasties in 40 cranioplasties. PEEK is a relatively new material used in cranial reconstructions and at the moment it is mainly used for secondary reconstructions. This may be the main reason why it shows a relatively high general complication rate, in particular infections. If PEEK could be used for the initial reconstruction the infection rate may be less because the overall health condition of the patient is better.
Using preoperatively planned and designed cranial implants, the operation time will be shortened because it is then possible to design and manufacture the cranioplasty before the operation. PEEK has a high biocompatibility, high chemical resistance and a low toxicity. PEEK does not have osseointegration abilities and thus no commensurately grow with the cranium will occur, so it seems that PEEK is not a preferable material in pediatric patients.

Titanium is also a material used for cranioplasties. It has a low infection rate, high biocompatibility and has biological inertness. On the other hand, it is radiopaque and conducts cold and heat. The costs of a titanium implant are relatively high. Current literature recommends titanium cranioplasties for the pediatric population. However, this material still seems to be suboptimal. Until the age of 20 years, the cranium grows physiologically. Before the age of 20 years a titanium cranioplasty is therefore not the optimal solution since it will not grow commensurately with the cranium. This may result in higher complication and reoperation rates and may require a new cranioplasty at a later age. This is also the case for PMMA and PEEK implants, and therefore these are not recommended for the reconstruction of cranial defects in growing children. Similarly, autologous bone appears to be suboptimal for cranial reconstruction in children due to the higher resorption and infection rates that were found in earlier studies in this population. Hydroxyapatite is reported to be a better option for the pediatric population, because of its ability to regenerate bone. Studies have proven that hydroxyapatite will convert into bone. An important disadvantage of hydroxyapatite is that it will remain brittle for a prolonged period of time (probably several months till years). This implies that the patient may not be sufficiently protected and needs to wear a helmet for a longer period of time.

**Optimization of the cranioplasty procedure**

Another challenge is to optimize surgical treatment of the reconstruction after a decompressive craniectomy. Different tools for further optimization were described in chapter 6. A 3D virtually designed template and mold can be used to generate a pre-planned outline of the defect and create an exact fit of the concomitantly manufactured cranioplasty. The surgeon follows the outline of the template to create the defect as planned. This may also be feasible in acute situations, as confection templates and implants can be used in for example primary trauma and in vascular emergencies.
Choosing an optimal treatment strategy for reconstruction of a skull defect after ablative tumor surgery presents another interesting dilemma for additional research. In these less acute situations, there is more time to plan preoperatively. Various techniques and timing of surgery have been described in literature for both soft tissue management and bony reconstruction. There is no standard treatment strategy for clinical decision-making in these low-volume high-complex cases. Patient and tumor treatment factors, such as (neo)adjuvant radiotherapy, prior treatments, medical history and comorbidity in frequently old and frail patients, may further hamper decision-making in reconstructing cranial defects. This is why an innovative technique was used in chapter 7 by applying a virtual pre-surgical 3D planning with the use of a patient-specific cranioplasty of PEEK. This technique aims for optimized control of the resection margin and less intra-operative dilemma’s. Wound dehiscence is still a feared complication in these cases. Since bone invasion is unpredictable and varying, an individual approach for calvarian reconstruction in every oncological case will be necessary. Adequate clinical reporting of larger case-series may produce guidelines for this patient group in the near future. Meanwhile, the different clinical, surgical and patient-specific aspects should be taken into account.

Towards a new material
Based on the current knowledge, an ideal material for cranioplasties should:

- be sterile and have anti-bacterial properties
- have osteo-inductive and/or osteo-conductive properties
- exert similar protective characteristics as human bone
- demonstrate no toxicity
- be easy to polish
- be easy to use intraoperatively
- have stable and consistent mechanical properties
- be easy for computer assisted additive manufacturing
- have low costs

In Chapter 8 different PMMA materials were investigated. This chapter showed that each of these materials, have their own release pattern of residual monomers. C&B MFH, a PMMA-based material designed for 3D printing, proved to have the lowest amount of residual monomers in total. The most residual monomers were released in the first hour for all materials investigated. If this material would be used for cranioplasties in the future, it is recommended to leave the cranioplasty in water at 37°C for at least 60 minutes to enable the residual monomers to leach out the material to reduce toxicity.
Another important characteristic is the ability to sterilize an implant. All cranioplasties should be sterile before they can be implanted in the patient. Chapter 9 investigated the effect of different sterilization protocols on different types of PMMA or PMMA-based materials. The sterilization method could significantly influence the material properties of cranial implants. We showed that ethylene oxide gas (EtO), hydrogen peroxide gas plasma (HPGP) and γ-irradiation are suitable techniques for the sterilization of PMMA without impact on the material properties. The use of γ-irradiation promotes the effective flexural strength and it seems that the material becomes stronger in a wet environment. Before a new material is used for creating a cranial implant it is important to also investigate the effect of the sterilization process on the mechanical properties of the material. Biological responses of the sterilization process are important, as the material surface may change due to the sterilization itself, with a possible different impact on the human tissue.

**FUTURE PERSPECTIVES**

Based on recently published literature it is plausible that the need for cranioplasties will increase in the future. Cranioplasties are necessary until bone-induction and/or bone-conducting methods are available. But as long as those medical devices are not developed for this purpose the patient still depends on a cranioplasty to ensure protection of the brain and to improve quality of life. As described in this thesis there is still a need for the development a new material for cranioplasty which includes the properties as mentioned above. Hence, we propose some studies that would contribute to a convincing, evidence-based answer on the question which material will be preferred for a cranioplasty.

A randomized clinical trial (RCT) should be conducted to gain further insight into the specific characteristics and biological behavior of different materials (titanium, PMMA, hydroxyapatite and PEEK) used in adult patients requiring a cranioplasty. Before commencing such an RCT, a Delphi Study is advocated to reach consensus on common procedures for cranioplasty. Important parameters to take into account in this study are:

- material used for cranioplasties
- use of antibiotics
- use of surgical drains
- post-operative wound care
- time interval between the decompressive craniectomy and cranioplasty with an alloplastic material.
The primary outcome measure of this future RCT needs to be subsequent implant loss, since this is particularly relevant for the patients involved. Additionally, morbidity, number of reconstructive surgeries or the need for permanent protection are important secondary outcome parameters.

Our systematic review described in chapter 2 showed that the usability of the material as perceived by the surgeons was not taken into account. Details about wound care were also lacking. These two aspects should be included in future research. In this RCT study the surgeon who performs the cranioplasty procedure should assess the usability of the material during surgery, the need for additional intra-operative adjustments and surgery time required to install implant. In general, the time of surgery corresponds with increasing infection rates. Wound care after cranioplasties has never properly been defined or studied in the literature. Variation in the wound care protocol may also affect infection rates. The design of the scalp incision is believed to influence complication rates and should therefore be recorded in the RCT study. The initial incision should be performed over unaffected bone, outside the area of reconstruction, to permit ideal soft tissue coverage and facilitate uneventful wound healing. On the other hand, incision and closure lines over an implant may lead to increased infection rates, especially in case of wound dehiscence.

Whilst patient recruitment in a RCT will take a substantial amount of time, the development of new materials for cranioplasties should not be discontinued in the meantime. Each PMMA subtype has a specific release pattern of residual monomers. To investigate what the effect of residual monomers is on human cells, particularly on cells of the dura and the effect on the surrounding bone, an in vitro study seems indicated. To optimize anti-bacterial properties and reduce infection rates of the cranioplasty, some innovations may be considered:

1) an anti-bacterial substance could be added to the cranioplasty material that elutes from the material cranioplasty;
2) little holes or corridors may be added in the cranioplasty material that are filled with anti-bacterial substance, which is slowly released from the material during the crucial period of healing time;
3) an anti-bacterial foam or spray that could be applied over the cranioplasty or parts of the cranioplasty to prevent the forming of biofilm and bacterial adhesion.
General discussion and future perspectives

THE NEXT STEP

The development of a new material for cranioplasty should tackle the current disadvantages.

Recent developments in Bioprinting may be provide a solution for the development of materials used for cranioplasties. The past decade 3D bioprinting has increased in popularity, as well as the applicability in clinical practice. A lot of research has been performed in this field over the past decade. 3D bioprinting is the utilization of 3D printing and 3D printing–like techniques to combine cells, growth factors, and biomaterials to fabricate biomedical parts that maximally imitate natural tissue characteristics. 3D bioprinting utilizes the layer-by-layer method to deposit materials known as bio-inks, extrusion-based bioprinting, laser-assisted bioprinting and even 4D bioprinting, to create tissue-like structures that are later used in medical and tissue engineering fields[18,19]. Wang et al. and Gao et al. both describe the first steps towards bone bioprinting. Wang et al. introduced the use of hierarchical porous and recombinant human bone morphogenetic protein-2(rhBMP-2)-loaded calcium phosphate nanoparticle/poly(L-lactic acid) (PLLA) nanocomposite scaffolds. The well-designed 3D printed scaffolds exhibited hierarchical porous structure and tunable osteoconductivity and osteoinductivity[20]. Gao et al. used acrylated peptides and PEG hydrogel with human mesenchymal stem cells for the formation of robust bone combined with cartilage[21].

If bioprinting could be used for the reconstruction of cranial defects, the patient’s own cells (e.g. stem cells) would ideally be used for the regrowth of a cranioplasty to replace the removed part of the skull. The anatomy of the human skull is complex because of its vascularity and multiple layers of bone. Apart from the complex anatomy the defects tend to be relatively large. Bioprinting a cranial reconstruction will therefore be challenging. To prevent bone resorption, a supplement developed from growth factors could be necessary to prevent the increased activity of osteoclasts.

Nowadays, bioprinting is relatively expensive, but it is expected that these costs will decrease in time. In the future this may become an affordable and stable solution for patient in the need for cranioplasty.
Chapter 10

A FUTURE CRANIOPASY PATIENT CASE

In the future the planning phase and manufacturing of cranioplasties should be easier, faster and cheaper. This may be realized in the near future by the introduction of several innovative changes in the workflow from craniectomy to cranioplasty and beyond. This is exemplified in the following scenario:

**Case:** A patient gets involved in a car accident. During the ride in the ambulance to the hospital, the neurological situation deteriorates.

**Phase I:** If the ambulance were to have the mobile equipment to perform a 3D scan of the head, an intracranial hemorrhage can be diagnosed. On arrival at the hospital, the intracranial pressure is measured to determine whether a decompressive craniectomy is indicated. A decompressive craniectomy with the optimal circumference is performed to either remove the hemorrhage or to lower the elevated pressure.

**Phase II:** After decompressive craniectomy, a patient-specific early recovery program starts. This program ensures an optimal condition of the patient and an early recovery. This can be realized by means of an adjusted diet, optimum pain control, motivation to quit smoking and drink alcohol and a good sleeping rhythm to improve the patient’s condition, with or without a (virtual) physical therapist. This program helps to reduce hospital stay, reduce postoperative complications, avoid stress and reduce insulin resistance. In the end this program reduces costs because of the limitation of the parameters described above.

**Phase III:** When the patient is neurologically stable and fit for surgery, the process of a new cranioplasty is started. First, a conversation with the patient and/or his family is needed to know the patient’s preferences concerning the choice of the material to be inserted. This helps in the decision for a material that best fits the patient, both literally and figuratively speaking. Patients should be aware of the advantages and disadvantages of the available options for reconstruction to facilitate a shared decision-making process. In the future artificial intelligence could probably be used to support the decision-making process.
Phase IV: All patients and surgeons will prefer a cranioplasty that has the highest accuracy, reliability and least complications. For this purpose a 3D scan (e.g. a CT scan or a MRI scan) of the cranial defect should be loaded in a dedicated computer program to design the optimal cranioplasty with a perfect fit and perfect aesthetics. Ideally, such a program should be able to virtually create the optimal cranial implant without human input. This might be possible with the use of novel algorithms using statistical shape models\textsuperscript{26}. Databases containing 3D data of a large number of healthy controls forms the bases for such a shape model. The available 3D data of the patient to be treated can be automatically analyzed using the developed statistical model. The statistical model will provide the optimal implant to cover the defect and create the 3D design of the implant automatically. After the implant has been created automatically in the computer program the design and fit in the skull defect can be demonstrated to the patient. Finally, a soft tissue simulation should be created by the computer program to illustrate to the patient how the esthetical outcome will be after surgery.

Phase V: Immediately after the design of the cranioplasty has been completed stem cells of the patient will be used for the production of the cranioplasty. This is combined with the artificial / newly developed extracellular matrix or mineral components of bone in a specially developed bioprinter and results in a cranioplasty made out of the patient’s own material.

Phase VI: During the re-opening of the cranial defect, the cranioplasty that has been manufactured using bioprinting can be inserted in the defect. The fixation of the cranioplasty to the skull will be without fixation of screws, but with the use of osteogenesis the cranioplasty will fixed soon to the surrounding bone.

Conclusion
This thesis has answered some important research questions and brought new insights on materials currently used for cranioplasties. Further standardization of definitions, diagnostic criteria, complications, standardized treatment protocols, and outcome measurements are still needed to ensure an evidence-based choice for materials in cranioplasties. Technological innovations and the development of new materials will be an important factor in improving the treatment of cranial reconstructions. The ultimate goal is to find an ideal and safe cranioplasty material for both patients and healthcare workers, with a low infection rate and long-term protection of the brain, preferably with limited costs.
REFERENCES


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