Clinical relevance of current materials for cranial implants

Towards an optimal patient-specific implant material

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CHAPTER 1

General introduction and outline of this thesis
GENERAL INTRODUCTION

The skull consists of the neurocranium and viscerocranium, it protects the brain, the source of cognition, logical thinking, imagination, creativity, emotion and memory. Protection of the brain by the skull is essential to the living human.

Decompressive craniectomy and cranioplasty

Decompressive craniotomy or craniectomy is a life-saving neurosurgical procedure in which part of the cranium is removed to reduce raised intracranial pressure (Figure 1A + 1B). This may result from, for example, cerebral edema or hemorrhage due to traumatic brain injury, cerebral infarction, subarachnoid hemorrhage, hemorrhagic strokes, neoplasms, or intracranial infections\textsuperscript{1–5}.

During a decompressive craniotomy the removed part of the skull is replaced back into the cranium during the same surgical procedure as the removal of the autologous bone\textsuperscript{6}. In some circumstances, this is not possible because of edema of the brain or persistently increased intra-cranial pressure. In such cases the removed part of the skull may be preserved and stored in a bone bank at temperatures as low as -84 °C\textsuperscript{7,8} or stored in a surgically created abdominal subcutaneous pocket in the patient\textsuperscript{8–11}. The autologous bone can be re-inserted when the patient has recuperated from the acute phase of illness and is neurologically stable\textsuperscript{5}. This procedure has the definition decompressive craniectomy.
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The reconstruction of calvarial defects is called a cranioplasty. In some cases the autologous bone may not be available because of multiple fractures, infection, resorption, depletion, or even discontinuation of an institutional bone bank due to increasing storage costs and (inter)national regulations\textsuperscript{12,13}. Therefore, artificial, alloplastic materials, for example titanium, poly (methyl methacrylate) (PMMA), hydroxyapatite (HA), and poly(ether ether ketone) (PEEK) are alternative materials to cover the remaining cranial defects\textsuperscript{13,14} (Figure 1C). The aim of the cranioplasty is to protect the brain, achieve a good cosmetic outcome, decrease neurologic problems and increase social performance\textsuperscript{12}.

It has been estimated that cranioplasties are performed at a rate of 25 patients per 1 million people. This – relatively- straightforward procedure remains challenging for surgeons because of the anatomy, aesthetics and functional contouring of the skull. A large number of short- and long-term complications after cranioplasties have been reported, including infection, hematoma and resorption. These complications results in medical, social and economic disadvantages and illustrate that there is no ideal reconstruction method or reconstruction material yet for cranioplasty.

The ideal material for cranioplasties should have specific requirements: good biocompatibility, easy to use, a satisfactory esthetic outcome, inexpensive, mechanical properties similar to human bone, ability to be sterilized, a low-infection rate, and the capacity to integrate with the surrounding bone.
History
Decompressive craniectomy and cranioplasty date back to the year 7000 BC and are among the oldest neurosurgical procedures in history, with a long-term evolution and a wide variety of materials. Cranioplasties have been discovered in many ancient civilizations including the Incas, the Britons, the Asians, the North Africans and the Polynesians. Around 2000 BC, a Peruvian skull was found with a hemi-cranietomy on the left frontal side of the cranium with a cranioplasty of a 1 mm thick gold plate in situ. At that time shells, gourds, and silver were also used for cranial reconstructions. The choice of material for cranial reconstructions likely depended on the social rank of the Peruvian citizen.

In 1505, the surgeon Ibrahim bin Abdullah was the first surgeon who wrote about the repair of cranial defects using goat and canine derivatives in his book ‘Wonders of Surgeons’ (Alâim-I Cerrâhin). This was followed by Fallopius (1523-1562) and Petronius (1565), who both used golden plates for the reconstruction of cranial defects. In 1668, Job Janszoon van Meekeren, a surgeon from Amsterdam, The Netherlands, was the first who described a successful cranial reconstruction in a Russian nobleman who sustained a sword injury to his head. The cranial reconstruction was performed with the skull of a dead dog. The recovery went perfect, but the nobleman was excommunicated from the Russian church, because of religious reasons it could not accept animal bone in a human skull. After this surgical intervention monkey, goose, rabbit, calf, and eagle bones were transplanted into the human skull, mostly after perforation and boiling the allograft in water. The use of ox horns, buffalo horns, and ivory also gave satisfactory results. However, better results were observed in autologous bone grafts. (Figure 2)
Figure 2: Overview of used materials for cranioplasties
Materials used for cranioplasties

Autologous bone

Von Walther performed the first human cranioplasty with autologous bone in 1821. Many other surgeons followed him: Ollier (1859), who believed that the periosteum was the most important tissue for bone regeneration. William MacEwen (1878) successfully inserted fractured calvarial bone and reinserted bone after trepanation. Seydel (1889) used tibial autografts for cranial repair, Muller (1890) developed the “sliding flaps” technique of the external tabula, and Beck (1906) introduced temporal muscle and fascia for the reconstruction of cranial defects. Dobrothworski (1911) used whole ribs, Röpke (1912) scapula, Mauclaire (1914) ilium, and split ribs were described by Brown (1917), all for the repair of cranial defects. Nowadays autologous bone is still used for cranioplasties. Autologous bone does not suffer from immune rejection, and bony ingrowth and revascularization have been observed. However, it is associated with a high risk of complications.

The most frequently mentioned complications for autologous bone flaps are infection and resorption. Infection ranges from 0% - 30% and is mostly caused by Staphylococci, especially S. Aureus. Resorption occurs in 0%-50%. Up till today the etiology of resorption is not fully understood. We do know that there is an imbalance between osteoblasts and osteoclasts, because of which parts of the autologous bone will disappear (Figure 3). These complications lead to high re-operation and removal rates of cranioplasties.

Figure 3: A patient who underwent a cranioplasty of autologous bone, after 18 months resorption was observed.
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Metals
For many years, metals have been used for cranioplasties. Booth and Gersten used aluminum and gold in 1890, Geib introduced vitallium in 1941, and tantalum was used by Pudenz and Odom (1942). In 1944, Boldrey discovered stainless steel mesh for cranial reconstructions followed by Scott, Wycic and Murtagh, who introduced a cranioplasty of stainless steel (1956). Thereafter, Simpson introduced titanium cranioplasties in 1965. Many other metals—or combinations—have been used, but most of them are replaced by stronger or better variants. Nowadays, pure metal cranioplasties are obsolete, except for titanium, mostly used as a mesh. Titanium mesh is light-weighted, rigid, has a biological inertness, and resists infection. One of the main disadvantages of titanium is the cause of imaging artifacts and scattering, and it easily conducts heat and cold, which can be a clinical issue. The rate of clinical (unwanted) exposure of the titanium mesh after reconstruction has been reported up to 42.2%.

Poly (methyl methacrylate) (PMMA)
The German chemist Dr. Otto Rohm patented Plexiglas in 1933, which became very popular. It was used in submarine periscopes and airplane canopies during war. Acrylic was primarily a substance used by dentists. The company Kulser (1936) introduced PMMA by mixing PMMA particles with a liquid monomer and benzoyl peroxide. After the dough stage, it was heated to 100°C and hardened in a stone mold. This discovery led to the use of PMMA for the reconstruction of cranial defects in monkeys (1939). Zander was the first surgeon who inserted a two-stage methyl methacrylate cranioplasty into a patient in 1940. Followed by Spence (1954), who developed a one-stage method for PMMA-reconstructions. Thereafter, during World War II, when the demand for cranioplasties was high, cranioplasties based on PMMA were frequently used.
PMMA is still one of the most frequently used alloplastic materials for cranioplasties\textsuperscript{18}. It is inexpensive, easy to use, and radiolucent. PMMA does not interact with the surrounding tissue, during the hardening process PMMA induces an exothermic reaction, consequently heating the adjacent tissues, is associated with a high infection rate, and controversies exist in literature about its toxicity\textsuperscript{14,18,26}. In the last years, a transformation of PMMA cranioplasties is observed. With the use of the CT-scan of the cranial defect of the patient, a mold of the cranial defect can be printed with additional manufacturing. During the cranioplasty procedure, the PMMA particles and liquid are mixed and placed into the mold. After a while, when the cranioplasty has cooled down, it is taken out of the mold. Adjustments can be made and is subsequently used for cranial reconstruction. This is an indirect method for additive manufacturing. Recent technology enables direct printing of an implant with higher accuracy, this is called a Patient Specific Implant (PSI).\textsuperscript{27}

\textit{Hydroxyapatite}

Hydroxyapatite is a substance made out of two different calcium phosphates, mixed with water. It has a hexagonal structure and is similar to human bone in composition and morphology\textsuperscript{28,29}. In 1952, Ray and Ward used synthetic hydroxyapatite crystals for the reconstruction of hips and legs of monkeys, dogs and cats\textsuperscript{30}. They discovered that the crystals used were transformed into new bone. Hence, they concluded that hydroxyapatite has the property to function as a matrix for bone generation\textsuperscript{30}. Hydroxyapatite was further developed by the American Dental Association in 1986 and became available for cranial reconstructions in 1996\textsuperscript{31,32}. It has a good osteoconductivity, biocompatibility and it is easy to use\textsuperscript{14,16,32}. Hydroxyapatite allows the expansion of the growing skull and results in incorporation into the surrounding bone\textsuperscript{16}. The process of the conversion of hydroxyapatite into bone takes time, which means that the material is brittle and may not sufficiently protect the brain\textsuperscript{16,17,33}.
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Poly (ether ether ketone) (PEEK)
PEEK is an organic thermoplastic polymer. It was introduced in the automotive and electrical industries before it was used for medical applications. In the nineties, PEEK became popular in orthopedics, trauma and spinal surgical interventions\textsuperscript{25,34}. In 2009 Hasanoso published one of the first cases using PEEK for cranioplasties\textsuperscript{35}. With the use of the patients CT-scan, the unaffected side can be mirrored and a symmetrical and aesthetically satisfying PSI patient-specific implant is manufactured using a milling technique\textsuperscript{36} (Figure 4). Nowadays, PEEK is an important polymer for medical devices, which is used in different fields of surgery. It has a high mechanical strength and biocompatibility, and does not deform below a temperature of at least 400\degree C\textsuperscript{34}. It has no cytotoxic activity, it does not induce adverse reactions to human tissues\textsuperscript{37}, and PEEK causes no artifacts in post-operative imaging. PEEK can be manufactured preoperatively as a PSI with satisfactory cosmetic outcomes and reduced operation time\textsuperscript{36}. PEEK does not have a bioactive potential\textsuperscript{38}. Unfortunately, PEEK is expensive\textsuperscript{39}, and controversy exists in literature about its effectiveness in covering larger defects as cranioplasty\textsuperscript{34,35}.

![Figure 4: Patient Specific Implant of PEEK](image)

Courtesy of Xiloc Medical, The Netherlands
AIMS AND OUTLINE OF THIS THESIS

This thesis is subdivided into four main parts, covering several aspects of the current materials for cranioplasties and the development and techniques of future methods and materials for cranioplasties: current evidence, current challenges, towards a new approach and toward the ideal material. This is followed by a general discussion of the contents of this thesis and future perspectives in this field.

Part II: Current evidence
The management of decompressive craniectomy and cranioplasty varies greatly between countries, hospitals and neurosurgeons. Regulations, e.g. national guidelines for bone banks and the recent European MDR (medical devices regulations) and costs with or without reimbursements from the government have a tremendous influence on the possibilities and choices for various techniques and materials. Many different materials have been developed and are being used in daily practice. In Chapter 2 all available evidence is summarized in patients who underwent cranioplasty using either autologous bone or alloplastic materials.

The principal outline of this thesis is to investigate and understand the clinical issues of different materials used for cranioplasties. If the individual factors can be identified that influence the clinical problems related to the current materials used for cranioplasties, more advanced materials may even be developed to reduce intra-operative and clinical complications.

Part III: Current challenges
The reasons for failure of existing materials for cranioplasty is important for the development of new materials. If the shortcomings are known, they may be camouflaged or even avoided. In part III of this thesis, different materials used for cranioplasties in clinical settings are explicated, in order to assess the advantages and disadvantages of the various materials.

After a decompressive craniectomy, a cranioplasty is mandatory to protect the brain and restore cranial esthetics. Autologous bone may be used for cranial reconstructions. However, reimplantation of preserved autologous bone is known to have a substantial risk of infection and bone flap resorption, not seldom resulting in loss of the autologous bone flap. In order to identify and quantify the risks of failure of autologous bone flaps, a two-center retrospective study is performed (Chapter 3).
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Patient-specific allogenic reconstruction is a typical example of advances in the medical technology. It demonstrates improvement of patient-relevant outcomes. With these technologies, it is possible to study and evaluate the corresponding clinical findings.

In Chapter 4, a PMMA (CMW-3) cranioplasty is described, which had been inserted in a patients' cranium 15 years ago, but had to be removed because of neurological complaints, most likely due to fracture of the implant. This case is evaluated by means of gel permeation chromatography (GPC), a micro-CT, finite element analysis (FEA) and flexural strength measurements.

The high infection and resorption rates have led to a search for superior synthetic materials for cranioplasties. In Chapter 5, a two-center retrospective study is described, including 38 patients who underwent 40 patient-specific cranioplasties of PEEK to detect possible complications and results.

Part IV: Towards a new approach

To improve the precise outlining of the cranioplasty and the aesthetic outcomes and to shorten operation time, different and relatively new intra-operative techniques may be used.

In Chapter 6, three cases are presented who underwent a cranioplasty of PEEK. The resection was guided with resection and control templates. Outcomes were compared with the original patient-specific planning and with 3D comparisons for form.

Squamous cell carcinoma with bony invasion into the scalp is a rarely described phenomenon in the literature. The optimal treatment strategy is still under debate. In Chapter 7 we present a patient with this anomaly. A novel comprehensive, one-stage surgical treatment is demonstrated and discussed.

Part V: Towards the ideal material

The properties of current materials for cranioplasties are important to understand and to progress to development of new materials. Part V of this thesis comprises two in vitro studies. Do different PMMA-based materials include different amounts of residual monomers? does sterilization has an effect on the mechanical properties of PMMA-based materials?
Various areas in healthcare use PMMA: orthopedics, dentists, maxillofacial surgery and neurosurgery. PMMA is cost efficient, radiolucent, light and easy to use. PMMA is formed through the polymerization of liquid methyl methacrylate (MMA) using PMMA powder as a filler to minimize shrinkage. Unreacted MMA (residual monomers) remains in the final product. However, the precise concentrations are still unknown for all PMMA-based materials. In Chapter 8, the amount of released, non-polymerized, monomers (residual monomers) is analyzed in four different PMMA-based materials with different compositions and fabrication methods (Vertex Self-Curing, Palacos R + G, DePuy CMW-3, and NextDent C&B MFH).

To reduce surgical time during polymerization the medical device may be manufactured before surgery with use of 3D imaging and additive manufacturing techniques. However, the created cranial implant still needs to be sterilized. This presents a challenge to assure optimal material behavior. Hence, in Chapter 9, four different sterilization methods (ethylene oxide, hydrogen peroxide plasma gas, autoclavation, and gamma-irradiation) are used for the sterilization of three different types of PMMA-based materials (Vertex Self-Curing, Palacos R + G and NextDent C&B MFH). To study the mechanical properties, the flexural strength, flexural modulus and impact strength were measured.

Part V General discussion
The overall findings of this thesis are presented in Chapter 10, in which the main results are summarized and discussed, followed by a description of the future perspectives.

Summaries of this thesis are presented in Chapter 11 in English and Dutch, respectively.
Chapter 1

References

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