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Correction of Skull Defects Using Hydroxyapatite Cement (HAC) – Evidence Derived from Animal Experiments and Clinical Experience

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Summary

Background. The development of satisfactory cranioplasty material and technique has been a continuing bio-engineering challenge. Cranial defects resulting from trauma, tumour or infection are most frequently reconstructed with nonviable alloplastic materials. At present, all synthetic or biological materials in the use for human cranioplasty are more or less ideal.

Methods. The in vivo properties of a fully resorbable bony substitute – hydroxyapatite cement (HAC, BoneSource®) are described in clinical investigations and animal experiments. HAC is prepared from calcium phosphate precursors which are hydrated and harden endothermically at 37 °C to form hydroxyapatite. Bone formation and resorption characteristics of HAC are examined in an adult minipig cranial defect model.

Findings. Cranial bone integrity has been restored in ten of eleven patients. Radiographic examination 6 months after surgery reveal a successful reconstruction of the skull defects. Sections of the cranial defect site from animals sacrificed at 12, 18 and 40 weeks demonstrate that new bone formation proceeds in HAC filled osseous defects. Histomorphological evaluation of HAC resorption and new bone formation indicates that HAC is nearly completely resorbed within 40 weeks and replaced by new bone with no loss in size or volume.

Interpretation. Hydroxyapatite cement (HAC) has an excellent biocompatibility (non-immunogenic and non-toxic), seems to be an optimal implant for cranial reconstruction and provides a biological scaffold for bone formation. However, further studies need to be conducted to determine the long-term stability of HAC.

Keywords: Hydroxyapatite cement (HAC); cranioplasty; cranial defects; bone substitute.

Introduction

Skull defects greater than 10 cm^2 situated in exposed areas of the cranial vault warrant elective cranioplasty to restore protection of the cerebrum and correct cosmetic defects.

Extensive efforts have been made to find the ideal material for craniofacial osseous defect repair that complies being a) biocompatible without eliciting inflammatory or reactive tissue response b) firm and stable for life c) non-allergic d) non-cancerogenous e) radio-lucent to allow unimpeded CT-scanning and MR-imaging f) strong enough to protect the brain and g) capable of facilitating bone ingrowth. The aforementioned criteria are fulfilled by hydroxyapatite cement (HAC) [18]. Hydroxyapatite (HA) represents the principal component of bone and comprises 60 to 70% of the calcified skeleton [3]. Meanwhile two types of HA are clinically established: a ceramic and non-ceramic preparation. For almost 20 years ceramic preparations have been in clinical use. Ceramic HA is synthetised in crystalline form at a low pH, then heated to 800 to 1300 °C in order to form a solid mass [3]. This heating process results in a hard, non-resorbable biomaterial which is not advantageous in facial plastic or reconstructive surgery as it is difficult to shape and does not permit fibro-osseous tissue ingrowth [3, 25]. Felsenfeld and co-workers [9] came to the conclusion, that only 17% of the pores within the ceramic hydroxyapatite preparation were filled by bone but 44% by soft tissue. These suggest that a close contact of ceramic preparation with bone is a prerequisite for an osseous union.

Hydroxyapatite cement (HAC; BoneSource®; Howmedica-Leibinger, Freiburg; Germany) differs substantially from the ceramic forms and is produced by direct crystallisation of HA in vivo. HAC does not require any heating for the formation of a structurally stable implant and can easily be moulded intraoperatively to cover precisely calvarial defects or to recreate a pre-existing contour for cosmetic support [2, 3].

The quest for a potentially viable, biocompatible and mechanically acceptable material for the reconstruction of skull defects prompted our clinical investigations and animal experiments with hydroxyapatite cement.

Methods

Hydroxyapatite cement is composed of tetracalciumphosphate and anhydrous dicalcium phosphate. These two components react isothermically in the presence of distilled water to hydroxyapatite at a physiological pH. Water is not part of the reaction in a stoichiometric sense; it provides the reaction vehicle that allows calcium and phosphate to dissociate and supersaturate the solution for hydroxyapatite precipitation [7]. The process of hydroxyapatite formation starts after setting the cement which takes 15 to 20 minutes [2]. The cement converts to hydroxyapatite (HA) within four to six hours and is no longer water – soluble after that time. For a successful application, HAC must be used as a dense paste and placed into a dry operative field; otherwise, the cement tends to absorb the ambient liquid and might lose its shape. Referring to the manufacturer's instructions, the proportion of the mixture is defined and the maximum amount of liquid must not be exceeded (5 g, 10 g or 25 g of BoneSource® powder was added to a maximum amount of 1.25–1.5 ml, 2.5–3.0 ml or 6.25–7.5 ml of sterile water appropriate to a powder-to-liquid-weight ratio of 3.3–4.0). Failure of this material was documented in case of a direct exposure to fluid e.g. cerebrospinal fluid during the setting process [19].

$$\underbrace{Ca_4(PO_4)_2O}_{\text{tetracalcium-phosphate}} + \underbrace{CaHPO_4}_{\text{calciummono-hydrogenphosphate}} \xrightarrow{[H_2O]} \underbrace{Ca_5(PO_4)_3OH}_{\text{hydroxyapatite}}$$

BoneSource®

Patients

In the last two years, 11 patients suffering either from an anterior fossa fracture combined with rhinorrhea [5], a complex, depressed fracture of the frontal bone [4], headache combined with a serious cosmetic deficit [1] or a tumour of the roof and lateral orbital wall underwent surgical closure of calvarial defects with HAC. The series included 9 men and 2 women, ranging in age from 16 to 73 years at the time of surgery. Exclusion criteria for the use of HAC were renal disease, pregnancy, prior local irradiation, proved metabolic bone disease, immunological abnormalities and impaired calcium metabolism.

All patients were followed by CT scanning and plain X-rays 6 months after surgery. All CT investigations included bone and soft tissue algorithms.

Case Report

Due to an acute loss of visual function, a 38-year-old woman underwent a surgical exploration of the optic nerve and optic chiasma through a pterional craniotomy. Because of a suspected aseptic osteonecrosis in January 1999, the patient was admitted to hospital. Furthermore, she complained about headache localised close to a right temporal craniotomy defect. A re-exploration was performed, the periosteum was carefully protected, the bony margins were renewed. Subsequently, the defects were filled and modelled with HAC in order to reconstruct the bony contour (Fig. 1a and b). After hardening the area was covered by the periosteum to facilitate the osteoconductive process. Pre- and postoperative frontal and lateral plain roentgenographs demonstrated the defect before and after application of HAC (Fig. 1c and d). Postoperative CT scans showed the corresponding calcareous area with the reconstructed temporal bone.

Animal Experiments

Four female adult minipigs (age: 24 months, body weight 48–75 kg) with completely pneumatized frontal sinus sustained craniectomy under endotracheal anaesthesia. The outer table of the frontal bone flap with the mucous membrane were discarded. Extreme care was taken to avoid injuries of dura and brain. Skull defects of different size (1.0×1.0 cm up to 3.5×2.5 cm) were closed by HAC (Fig. 2a and b). Due to limited shear resistance of HAC, we evolved a so-called "hammock plastic" in cases of large craniotomy defects. Subsequent to the craniotomy, the skull defect was covered by a suitable sheet of Ethisorb® (a mesh consisting of vicryl (polyglactin 910) and polydioxanone PDS produced by Ethicon, Norderstedt; Germany) fixed at the bony margins. After 12, 18 and 42 weeks the animals were sacrificed, the entire nasofrontal sinus complex was en bloc resected in order to perform histological investigations. Prior to preservation with formalin CT-scanning was performed. According to the method described by Donat and Breuer [6] for the investigation of undecalcified bone the skull is embedded in Kulzer resin (Technovit 7200 VLC). The area which should be investigated is situated on the block surface. After mounting on a slide the surface is ground and polished using a micro-grinding system (Exakt-Apparatebau, Norderstedt, FRG). The surface of the specimen gets mounted on a planparallel plastic slide and sectioned at 100 µm. Finally, these sections get ground and polished to a thickness of 10 µm. Histological preparations of the former defect regions were obtained, dyed with toluidine blue and finally histomorphologically analysed using the light and polarising microscope. Additionally undyed histological specimen were examined by means of a fluorescence microscope [1].

The study protocol was approved by the animal care and use committee.

Results

With the exception of one case, healing was uneventful ($n = 10$). A re-exploration was necessary in one patient with a frontally contaminated laceration underlying a comminuted cranial fracture, although wound debridement and antibiotic treatment preceded. No patient developed scalp effusions, hematomas or CSF fistula postoperatively. None of the implants became exposed or extruded. Hydroxyapatite cement can be moulded intra-operatively and sets isothermically to microporous hydroxyapatite, so that it can be either used for full thickness calvarial reconstruction or by replenishing the lamina externa or interna cranii with HAC. No special fixation elements e.g. screws, microplates or suture materials are necessary to fix the hydroxyapaptite cement.

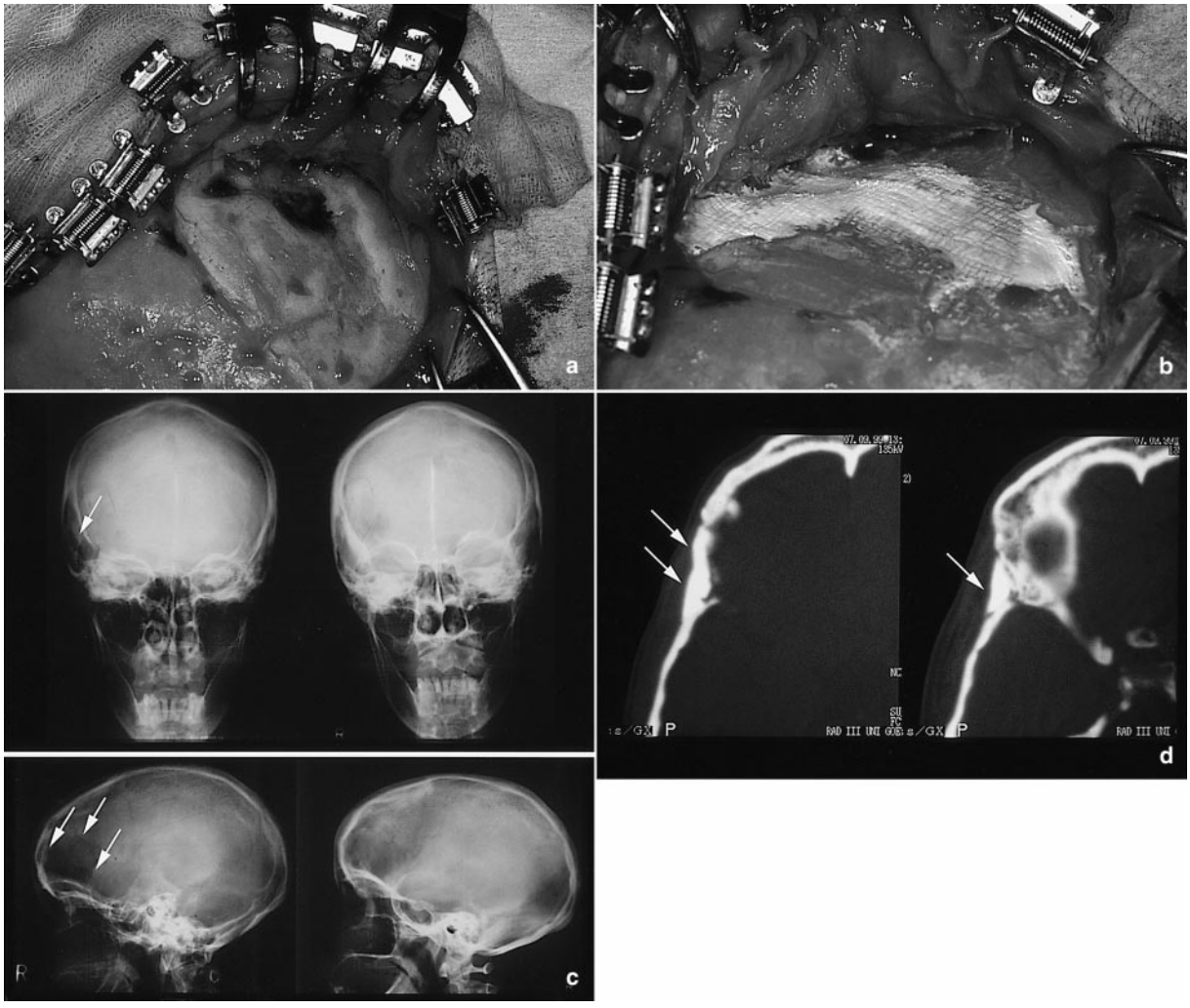

Fig. 1(a, b) Intra-operative site of the 38-year-old woman with a cosmetically disfiguring defect after pterional craniotomy. Placement of HAC and complete correction of the defect. (c) Pre- and postoperative frontal and lateral plain roentgenographs demonstrate the defect before and after application of HAC (white arrows). (d) Postoperative CT scans show the corresponding radio-opaque HAC filling the defect homogeneously

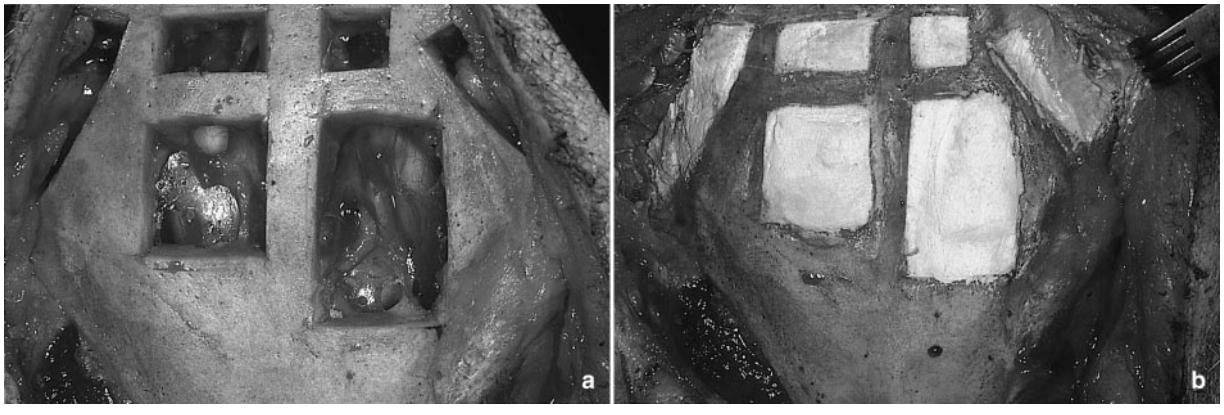

Fig. 2(a) Intra-operative site of a minipigs: Four skull defects of different size directly after craniotomy. (b) Skull defects of an adult minipig reconstructed by hydroxyapatite cement (BoneSource®)

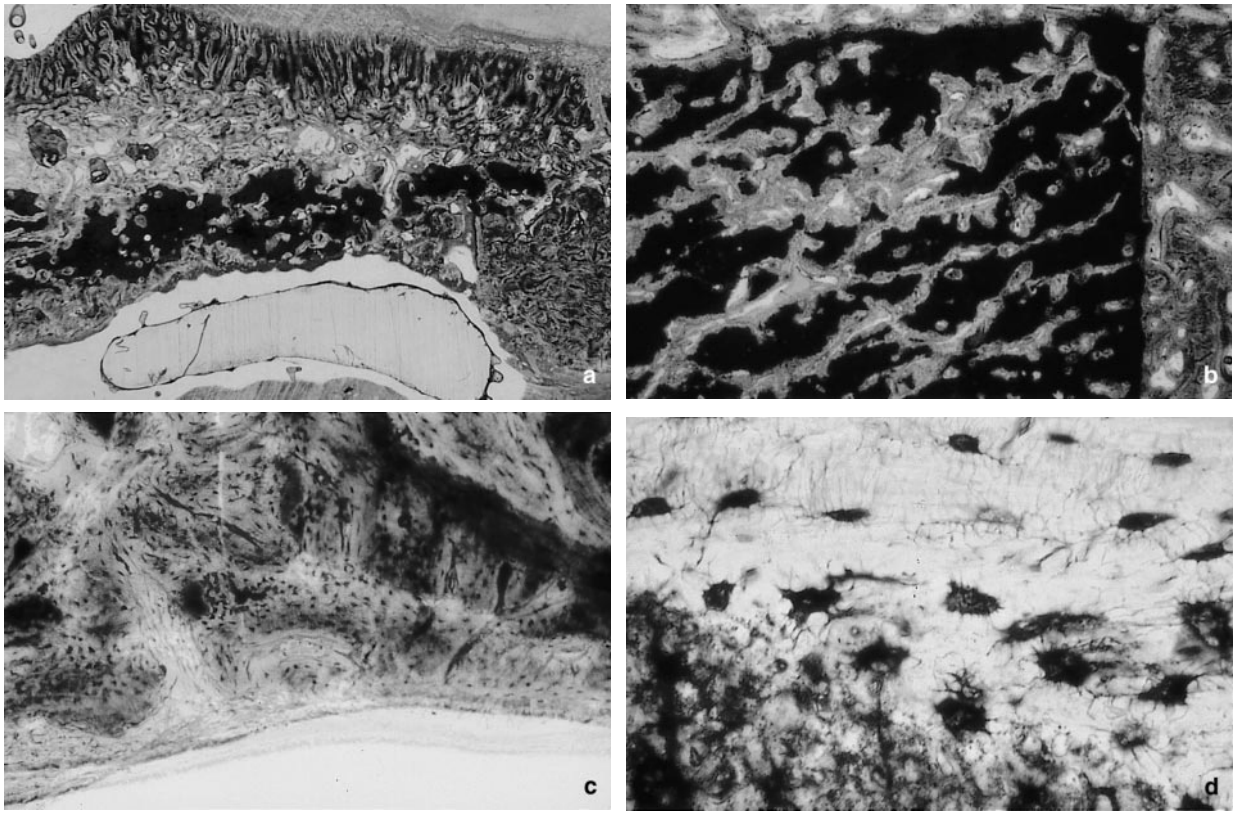

Fig. 3(a) Toluidine-blue-stained section of an adult minipig (frontal bone; magnified 3.5 times) 12 weeks after implantation of HAC confirming a progressive growth of new bone into the pure hydroxyapatite cement. New bone ingrowth started at the implant periphery adjacent to the diploe of the surrounding skull. Non-resorbed residual HAC is seen as black granular material surrounded by new trabeculae of bone. (b) Toluidine-blue-stained enlarged section (Fig. 3a) of an adult minipig (frontal bone; magnified 25 times) 12 weeks after implantation of HAC. Defect boundaries are along the right hand edge. Non-resorbed or residual HAC material is discernible as distinct black islands within the trabecular bone. (c) Toluidine-blue-stained enlarged section (Fig. 3a) of an adult minipig (frontal bone; magnified 25 times) 12 weeks after reconstruction of the defects with HAC confirming a bland mucous membrane covering the HAC. (d) Toluidine-blue-stained enlarged section (Fig. 3a) of an adult minipig (frontal bone; magnified 200 times) 12 weeks postimplantation demonstrating a physicochemical integration of the osseous substitute and resorbed HAC. Active bone remodelling was observed characterised by the presence of active osteoblasts and mature osteocytes at the interface. Large single cells along the bone spicules were considered to be osteoblasts

Six months after surgery, HAC appears densely radio-opaque on plain radiographs and CT scans. Small amounts of HAC, such as a thin layer applied to repair a small defect of the frontal lamina externa cranii (outer table of cranial bones), are quite subtle and cannot be separated from native bone, even by CT scans. An intermediate amount of HAC sealed the middle ethmoidal sinus. In order to identify HAC, bone algorithms are superior to soft tissue algorithms on CT scans. On tissue algorithms, HAC does hardly differ from native bone.

All animals in the experimental study survived the duration of the experiments. There were no wound infections or wound-related complications. On gross examination, the hydroxyapatite cement – bone implants were intimately incorporated into surrounding bone. The reconstructed outer table of the frontal bone maintained its appearance. The histological examinations of the adult minipigs demonstrated a progressive ingrowth and replacement of existing HAC by host bone without foreign bodygiant cell formation.

At week 12, the boundary between bone and the HAC was clearly visible. Non-resorbed or residual HAC material is seen as distinct black islands within the trabecular bone (Fig. 3a and b). The HAC islands were found to be traversed and penetrated by significant new bone. In this early stage a mucous membrane covering the undersurface of the implant is confirmed although the mucosa has been initially resected (Fig. 3c). New bone formation could also be seen to extend from the external surfaces possibly due to vascularized and functioning periosteum covering the implant.

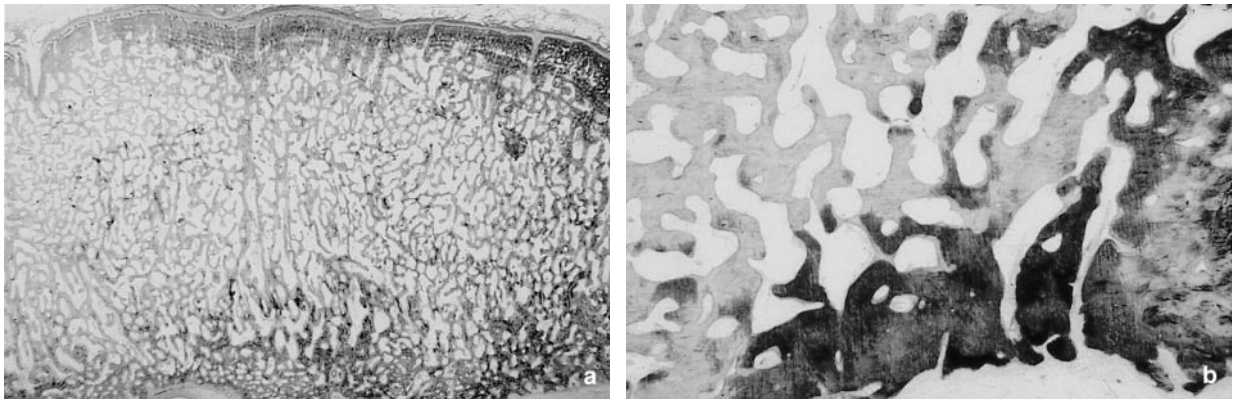

Fig. 4(a) Toluidine-blue-stained section of an adult minipig 40 weeks postimplantation (frontal bone; magnified 1.3 times) confirming a subtotal resorption of the HAC. Note the marked subperiostal coarse-fibred osseous matrix neighbouring the HAC-material. (b) Toluidine-blue-stained section of an adult minipig 40 weeks after application of HAC (frontal bone; magnified 5 times). Some residual implant (HAC; dark grey material) persists following decalcification

Presumptive osteoblasts and osteocytes were observed in intimate association with non-resorbed HAC (Fig. 3d). Histologically, the bone replacing HAC was more dense than the lamellar bone of the sinus walls. Replacement of HAC by bone appeared to progress from the periphery adjacent to the diploe, where the cement was in contact with the bone, toward the center of the implants.

After 18 weeks, the defect healed with bone that was not yet fully aligned as analysed by polarising microscopic methods. These investigations verify – despite an early bony substitution of the HAC – a non-physiological anisotropy due to irregular formation of intra-osseus collagen fibers leading to a reduced biomechanical load-bearing capacity. With increasing substitution of the osseous regenerate and remodulation of HAC a shearing force dependent orientation of the intra-osseus collagen fibers became apparent.

By 40 weeks, the restoration of native bone morphology was nearly complete. The defect was filled with normal bone and the defect edges were not precisely delineated by any staining or histomorphological method used. Residual HAC, when observed, was found as discrete fragments (Fig. 4a and b). Due to the results of our animal experiments we do not expect sufficient stability of the cranioplasty with HAC until 36–40 weeks. However, the time of conversion into firm bone is dependent on the implant or the defect size. Replacement of hydroxyapatite cement implants by new bone is postulated to occur by a combination of osteo-integration and implant resorption. No loss of implant volume or change in external contour was detected.

Discussion

The development of cranioplasty materials and techniques has been a persisting medical and bioengineering challenge as spontaneous repair of adult cranium in mammals is limited. In the past, various materials have been used for the surgical repair of facial bone or skull base defects including sea shells, animal horn, ivory, gold, silver, heterologous or autologous bone and cartilage, platinum, vitallium, tantalum, stainless steel, titanium, plexiglas, acrylic resin and silastic [4, 5, 8, 10, 11, 16, 20, 24, 26].

Only few implants have proved to be appropriate and convenient in practice. Due to the complex interaction between body and implant synthetic materials frequently fail to be integrated into surrounding tissues or might be degraded over time.

As an alternative, autogenous exteriorised calvaria are kept frozen and preserved for delayed re-implantation [21]. Although the re-use of autologous bone is advantageous these preserved autografts are later remodelled. The frequent predominance of resorption over new bone formation results in a smaller, less protective template [22]. As adult membranous bone does not regenerate the re-implantation of a replaced bone flap might be complicated by an aseptic absorption in up to 15% of cases or by late infection [13].

With the exception of polymethylmethacrylate

(PMMA; Palacos®, Merck, Darmstadt, FRG), the above mentioned materials (e.g. platinum, vitallium, titanium) cannot be easily formed or shaped. PMMA – the most widely used material for the reconstruction of skull defects [12, 23] – is a viscous chemical polymer that can easily be shaped for approximately 5–7 minutes. PMMA turns into a very hard material however, the polymerisation phase is highly exothermic generating temperatures up to 110 °C [14, 27]. Any tissues in contact with the cement would be susceptible to thermal necrosis. As a serious disadvantage, PMMA can cause a significant inflammatory response resulting in foreign-body giant-cell formation, fibrous encapsulation of the implant and late perennial infection.

However, HAC is characterised by most desirable properties such as biocompatibility, osteoconductivity, resistance to infection, good adhesion to surrounding bone and volumetric stability. For successful treatment, HAC is used as a dense, cement-like paste. Therefore, water has to be added drop by drop in order not to exceed the permissible maximum of solvent. When the paste hardens, a stable implant is obtained in approximately 15–20 minutes [2, 3, 7]. During the next 4–6 hours the self-setting cement becomes water-insoluble as the material converts to hydroxyapatite. The endothermic nature of the HAC setting process results in extended ease of use. HAC does not require further fixation either by suture material or screws or miniplates. At this time, although HAC has good compressive strength, the bony substitute has limited shear resistance and is therefore only appropriate for the use in non-stress-bearing applications [3].

Over the subsequent months, native bone grows into the pores of the HAC and forms a strong bond in a process called osseo-integration. After implantation, new bone was formed concomitantly with resorption of the substitute (BoneSource®) [2]. The newly formed bone appeared to be effectively remodelled over time, producing lamellar bone nearly indistinguishable from normal, mature osseous tissue. Although the process of HAC resorption was not explored, a number of observations suggest that a remodelling mechanism of normal cellular bone may be involved [15]. This includes the formation of new bone interspersed within residual HAC islands, the identification and ingrowth of presumptive bone forming cells, the vascularisation of cell clusters and the continuity of HAC with the newly shaped bone. HAC is recognised by the bone remodelling apparatus as being substantially the same. Interestingly, the resorption and replacement of HAC by bone occurs not only from the outer edges of the HAC. The process of remodelling seems to gain access to the interior of the HAC material (see Fig. 4a). Up to now, the reason for these findings is unknown. Perhaps the micro-porosity of HAC facilitates the migration of cells into the HA material [2]. The results of our animal experiments led to the conclusion that the presence of HAC stimulates bone formation and healing. The resorption characteristics of this substitute and its replacement by natural bone has significant implications because the use of a resorbable osseous substitute leads to restoration of bone with original biomechanical qualities. On the other hand, it has to be taken into consideration that in the first weeks after application HAC is mechanically not as strong as normal bone or ceramic hydroxyapatite blocks. HAC gains strength during the process of conversion and osteo-integration. However, for non-weight-bearing sites, such as facial bones or skull base, this is not an important limitation.

Meanwhile, few reports of unsuccessful treatment with HAC were published [17, 19], where the HAC implant was re-absorbed. Once the paste has been contoured to the defect, it is imperative to keep the surgical field surrounding the implant dry for proper setting of the hydroxyapatite cement. After meticulously performed haemostasis, a relatively waterless operative field can be achieved by continuous suction, placing dry gauze or cottonoids for absorption and suction drains into the wound to allow the implant to set properly and to decrease excess fluid around the wound.

Exposure to a water-based medium during this period will result in an incomplete setting of HA – crystals and redissolution with subsequent implant resorption. If the substance is used as indicated in the package insert HAC can be safely administered and recommended for the repair of cranial defects. Further investigations are needed to get to know the long-term stability of HAC and its strength with respect to trauma.

Conclusion

HAC possesses superior features concerning the reconstruction of cranial defects due to the ease of application, lack of inflammatory response and its osteointegrative and osteoconductive capacity when placed in contact with bone or periosteum. Hydroxyapatite

cement is easy to handle intra-operatively and can accurately be shaped to reconstruct the contour of the calvarium.

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Comments

The authors describe the use of hydroxyapatite cement for cranial reconstruction in animal experiments and clinical investigations.

Cranial defects of different sizes were created in four pigs and filled with hydroxyapatite cement. Complete healing of the hydroxyapatite cement implants was macroscopically evident in all cases. Microscopic examinations revealed that new bone had almost completely replaced the hydroxyapatite cement in the course of about 40 weeks.

In a clinical setting, a total of 11 patients with a cranial defect received a hydroxyapatite implant. An infection developed in one case, but implant healing was uneventful in all others. The hydroxyapatite-cement-filled cranial defects appeared radiopaque at follow-ups performed after 6 months.

The experimental and clinical studies investigate potential applications for hydroxyapatite cement in neurosurgery. This is a promising implant material, since it is replaced by new bone in the course of several months. The study results reveal advantages over the hitherto applied implantation of methylacrylate cement or titanium mesh for indications like bone defects due to traumas or tumors. However, this new procedure has not been directly compared with the techniques routinely applied thus far. Moreover, no long-term experience has been gained. Hydroxyapatite cement only appears to be useful for replacing autologous bone that has become autolytic or infected.

M. Brock

In the most diversified specialties a great number of efforts have scientifically been made to find an extensively ideal material for bone replacement to avoid the morbidity of graft harvesting. Great biological demands should be made on such materials for bone substitutions. They should be biocompatible, not eliciting inflammatory effects, not evoking allergic reactions and not being cancerogenic. As an ideal prerequisite a lifelong stability should be required, rendering a slow substitution by native bone feasible. Hydroxylapatit has been used for a long time in the field of maxillofacial surgery as material for bone substitution and proved to be beneficial in various cases.

Hydroxylapatite cement (HAC, BoneSource®) was examind in

this animal experimental study and the first clinical experience was presented. Four female adult minipigs with an extradural frontal bone defect sustained craniectomy. The defect was closed with HAC and in addition, covered with a suitable sheet of Ethisorb®. After 12, 18 and 42 weeks the entire nasofrontal sinus complex was resected en bloc and examined under a fluorescence microscope histomorphologically. None of the HAC implants were infected and were integrated uneventfully into the surrounding bone. A progressive ingrowth and substitute of the HAC by the native bone with no foreign-body reaction was detected histologically. The substitute with HAC was closed almost complete histomorphologically after 42 weeks. The original defect was therefore covered by bone, which continously merged into the neighbouring bone.

Eleven patients sustaining a fracture of the frontal skull base with rhinorrhea or a fracture of the frontal bone were evaluated in the clinical study. Two case reports were presented including several pictures. With the exception of one patient suffering from a frontal contaminated laceration, healing was uneventful in all the HAC implants. Six months postoperatively the HAC-radio opaque could be detected both radiologically and in the CT-scan.

Based on these investigations it could be assumed that HAC is suitable as cranioplasty material for bone replacement, substituting the range of alloplastic materials known so far.

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