Clinical relevance of current materials for cranial implants

Towards an optimal patient-specific implant material

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Citation for published version (APA):
A systematic review of the safety of autograft and allograft materials for cranioplasties


This chapter is based on the publication: Autologous bone is inferior to alloplastic cranioplasties
Safety of autograft and allograft materials for cranioplasties, a systematic review

Published: World Neurosurgery, 2018
ABSTRACT

Background: Currently, various materials are routinely used for cranioplasty after decompressive craniectomy, each with their own features, potential benefits, and harms.

Objectives: To systematically review available literature about safety (infection, resorption, and removal) of different materials used for cranioplasty for any indication.

Methods: A comprehensive search in MEDLINE, EMBASE, and the Cochrane library was performed for relevant studies published up to January 2017. Study quality was assessed according to the Cochrane Collaboration risk of bias assessment tool, and a set of 27 predetermined parameters was extracted by 2 investigators independently for further analysis.

Results: The search yielded 2 randomized, 14 prospective, and 212 retrospective studies, totaling 10,346 cranioplasties in which 1952 (18.9%) complications were reported in patients between 0 and 90 years old. Overall, study quality was low and heterogeneity was large. Graft infections and resorption were most prevalent: overall infection rate was 5.6%. Autologous cranioplasties showed an infection rate of 6.9% versus 5.0% in combined alloplastic materials, including poly(methyl methacrylate) with 7.8%. Resorption occurred almost exclusively in autologous cranioplasties (11.3%). The greatest removal rate was reported for autologous cranioplasties (overall: 10.4%), which was significantly greater than that of combined alloplastic materials (overall: 5.1%; risk difference = 0.052 [95% confidence interval: 0.039–0.066]; NNT = 19 [95% confidence interval: 15–25]).

Conclusion: Available evidence on the safety of cranioplasty materials is limited due to a large diversity in study conduct, patients included, and outcomes reported. Autografts appear to carry a greater failure risk than allografts. Future publications concerning cranioplasties will benefit by a standardized reporting of surgical procedures, outcomes, and graft materials used.
INTRODUCTION

In patients who underwent a decompressive craniectomy, a cranioplasty is commonly required to protect the brain, restore aesthetics, relieve neurological symptoms, as well as for psychosocial reasons\textsuperscript{1}. The number of cranioplasties performed has increased over the last years, reaching 20-25 per million inhabitants per year in 2010 (in Europe, Middle East and Africa)\textsuperscript{2}.

Autologous bone is widely used for cranioplasty, relatively inexpensive, easy to obtain, exhibits good fit and contour, presents no risk of disease transmission and is viable\textsuperscript{3}. Bone resorption and infection are the most frequently reported complications, with a large range in degree, timing and occurrence\textsuperscript{4-6}.

In the past, some cranioplasties were manufactured by molding autologous bone grafts in alginate or plaster. Poly (methyl methacrylate) (PMMA) was cast into the mold and polymerized to avoid the exothermic reaction occurring adjacent to the brain during hardening\textsuperscript{7,8}. Currently, PMMA is also used in a customized 3-dimensional (3D) mold to achieve better cosmetic results\textsuperscript{9}. Autologous bone may not be available because of fracture, infection, resorption, depletion, or even discontinuation of an institutional bone-bank due to increasing storage costs and (inter)national regulations. In these cases alloplastic materials may be used, e.g. titanium, PMMA, hydroxyapatite (HA), and poly(ether ether ketone) (PEEK)\textsuperscript{2,10-12}.

Computer-aided design and computer-aided manufacturing (CAD/CAM) and other 3D virtual planning technologies have been applied to overcome the shortcomings of intraoperative molding and allow for the creation of patient-specific implants (PSI). A PSI aims for a perfect fit as the design is based on the patient’s computed tomography (CT) or cone-beam CT data. More sophisticated materials enable manufacturing by 3D printing and rapid prototyping techniques, allowing for more complex shapes when personalized and unique shapes are required\textsuperscript{13,14}. Consensus on the preferred method or material is lacking. The ideal material is similar to cortical bone, biocompatible, radiolucent, nontoxic, has a low complication rate, is easy to use in the operation room, can be used to create an optimal PSI, brings excellent cosmetic results, and is low in cost\textsuperscript{10}.
Many studies have been published regarding the possible benefits and potential risks or risk factors of complications after cranioplasty. However, no all-encompassing review has been published to this date. This comprehensive review summarizes all available evidence in patients who underwent cranioplasty using either autologous bone or alloplastic materials regarding their safety, to aid evidence-based decision-making.

**MATERIAL AND METHODS**

**Search strategy**

This systematic review was conducted using the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines, methodological standards outlined in the Cochrane Handbook for Systematic Reviewers and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria (Figure 1). A systematic search of the literature was conducted in MEDLINE, EMBASE and the Cochrane library from their inception until January 26, 2017. Search terms included MeSH-terms in PubMed and EMtree, as well as free text terms. For the Cochrane library free text terms were used. The full search strategies for each database are shown in Supplementary Table 1.

**Selection process**

Two reviewers (S.V. and T.M.) independently screened all potentially relevant titles and abstracts for eligibility. If necessary, the full text article was checked for the eligibility criteria. Articles were included if they met the following criteria: 1) clinical patient study; 2) a cranioplasty was performed or; 3) a craniectomy in combination with cranioplasty or; 4) a craniotomy with alloplastic material for any patient and any indication and; 5) were written in, or translated to, a Western European language.

Studies were excluded if: 1) the surgical intervention was a craniotomy with simultaneous replacement of the autologous bone graft; 2) non-clinical articles (technical notes, animal studies, laboratory studies, letters, systematic reviews); 3) 6 or more materials were used; or 4) primary outcomes were not reported per material. Disagreements were resolved by consensus or discussed with a third reviewer (D.U.). After the first selection the full text of the articles was obtained for further review.
Autologous bone is inferior to alloplastic cranioplasties

**Quality assessment**

Methodological quality of the included papers was assessed by a validity questionnaire on the individual studies using the Cochrane Collaboration tool for assessing risk of bias.9
Data extraction

The primary safety outcomes are defined as ‘infection’, ‘resorption’ and ‘removal’ rates.

From the selected articles the following parameters were extracted, if reported, on a pre-defined data extraction form: 1) study design; 2) number of patients; 3) number of cranioplasties; 4) cranioplasty material used; 5) sex; 6) age; 7) comorbidities; 8) smoking; 9) indication for cranioplasties; 10) previous cranioplasties; 11) location of the surgical intervention; 12) size of the defect in cm²; 13) use of antibiotics; 14) use of a drain; 15) involvement of the frontal sinus; 16) operation duration; 17) time interval between decompressive craniectomy and cranioplasty; 18) use of a mold, 3D printing or computer-aided design and computer-aided manufacturing; 19) all reported complications; 20) complication policy; 21) time interval between occurrence of complications and cranioplasty; 22) bacterial strain as cultured from the site of infection; 23) quality of life (QoL) measures; 24) esthetic outcome; 25) neurological functioning; 26) follow-up duration; 27) drop-outs. All data were extracted and verified by two authors (S.V. and T.M.) independently. Timing was recalculated to months according to the Gregorian calendar.

Data analysis

Descriptive analysis of the included studies, outcome analysis, assessment of heterogeneity, and any subgroup analysis were performed using IBM SPSS v.24 (IBM Corp., Armonk, New York, USA).

If clinical heterogeneity was limited, a meta-analysis would be performed. Subgroup analysis was planned for each of the cranioplasty materials, and autologous versus alloplastic materials, regarding the primary outcomes. Differences in dichotomous outcomes are described as risk ratios (RRs), risk differences (RDs) and numbers needed to treat (NNTs), each with their 95% confidence intervals (95%CIs). Differences in continuous outcomes are reported as mean differences and their 95% CIs or medians with their interquartile ranges (IQRs). If the included studies are clinically heterogeneous, a range is provided of the outcomes for each of the cranioplasty materials.
RESULTS

Characteristics of included studies
The literature search yielded a total of 5683 eligible papers, of which 228 were eventually included in this systematic review (Supplementary Table 2).

Of the 228 included studies, 212 (93.0%) had a retrospective design. Two hundred one were case series, 20 case reports, 5 cohort studies, and 2 randomized clinical trials. Studies were published between 1952 and January 2017 and were conducted on 6 continents, whereas most of them (216; 94.7%) originated from North America, Europe, or Asia.

Many studies were flawed in their reporting of outcomes; even basic information, such as patient age, sex, or indication for cranioplasty, was not reported in all cases. Only 4.8% of the studies reported on smoking behavior of their patients, whereas 82.5% of studies described the patient’s sex (Table 1).

Included studies were quite heterogeneous due to a large variability in surgical procedure, outcome definitions, and patient details. Therefore, no meta-analysis could be performed.

Study sizes ranged from 1 to 672 cranioplasties, totaling 10,346 cranioplasties. In 193 studies a single material was used for cranioplasty, whereas in 35 two or more materials were used (Table 2). Autologous bone was the most frequently used material for cranioplasty (n=3335 cranioplasties), whereas PEEK was infrequently used (n=250 cranioplasties). In 112 (60.2%) studies the mean follow-up was longer than 1 year. Complications of cranioplasties were reported in 220 studies. Overall, reported complications ranged from wrinkle formation and vomiting to death, without a clear threshold as to the definition of a complication.

Neurological function assessment after cranioplasty was reported in 44 studies, of which 22 used a numerical scale. The Glasgow Outcome Scale (GOS) was reported in 9, The Glasgow Coma Scale (GCS) in 17 occurrences, and 1 study used the House-Brackmann scale.

Autologous bone is inferior to alloplastic cranioplasties
### Table 1: Demographics of the included cranioplasties (n= 10,346)

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Mentioned in study (%)</th>
<th>Total (%)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (male)</td>
<td>188 (82.5)</td>
<td>4191 / 7749 (54.1)</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>200 (87.7)</td>
<td></td>
<td>0-90</td>
</tr>
<tr>
<td>Comorbidities</td>
<td>32 (14.0)</td>
<td>1844</td>
<td></td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td></td>
<td>51 (2.8)</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td></td>
<td>78 (4.2)</td>
<td></td>
</tr>
<tr>
<td>Obesity</td>
<td></td>
<td>7 (0.4)</td>
<td></td>
</tr>
<tr>
<td>Preoperative radiotherapy</td>
<td></td>
<td>116 (6.3)</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td></td>
<td>133 (7.2)</td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td>11 (4.8)</td>
<td>122 (10.8)</td>
<td></td>
</tr>
<tr>
<td>Initial diagnosis</td>
<td>209 (91.7)</td>
<td>8148</td>
<td></td>
</tr>
<tr>
<td>Trauma</td>
<td></td>
<td>3352 (41.1)</td>
<td></td>
</tr>
<tr>
<td>Cerebrovascular</td>
<td></td>
<td>2100 (25.8)</td>
<td></td>
</tr>
<tr>
<td>Infection</td>
<td></td>
<td>222 (2.7)</td>
<td></td>
</tr>
<tr>
<td>Tumor</td>
<td></td>
<td>1365 (16.8)</td>
<td></td>
</tr>
<tr>
<td>Revision reasons</td>
<td></td>
<td>31 (0.4)</td>
<td></td>
</tr>
<tr>
<td>After autologous bone</td>
<td></td>
<td>266 (3.3)</td>
<td></td>
</tr>
<tr>
<td>Epilepsy</td>
<td></td>
<td>5 (0.1)</td>
<td></td>
</tr>
<tr>
<td>Congenital deformation</td>
<td></td>
<td>261 (3.2)</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td></td>
<td>546 (6.7)</td>
<td></td>
</tr>
<tr>
<td>Site</td>
<td>98 (43.0)</td>
<td>3032</td>
<td></td>
</tr>
<tr>
<td>Unilateral</td>
<td></td>
<td>2720 (89.7)</td>
<td></td>
</tr>
<tr>
<td>Bilateral</td>
<td></td>
<td>101 (3.3)</td>
<td></td>
</tr>
<tr>
<td>Bifrontal</td>
<td></td>
<td>211 (7.0)</td>
<td></td>
</tr>
<tr>
<td>Location</td>
<td>116 (50.9)</td>
<td>4102</td>
<td></td>
</tr>
<tr>
<td>Frontal</td>
<td></td>
<td>627 (15.3)</td>
<td></td>
</tr>
<tr>
<td>Frontotemporo-parietal</td>
<td></td>
<td>535 (13.0)</td>
<td></td>
</tr>
<tr>
<td>Temporo-parietal</td>
<td></td>
<td>79 (1.9)</td>
<td></td>
</tr>
<tr>
<td>Parieto-occipital</td>
<td></td>
<td>12 (0.3)</td>
<td></td>
</tr>
<tr>
<td>Fronto-temporal</td>
<td></td>
<td>538 (13.1)</td>
<td></td>
</tr>
<tr>
<td>Temporal</td>
<td></td>
<td>427 (10.4)</td>
<td></td>
</tr>
<tr>
<td>Fronto-parietal</td>
<td></td>
<td>70 (1.7)</td>
<td></td>
</tr>
<tr>
<td>Fronto-temporo-parieto-occipital</td>
<td></td>
<td>1 (0.0)</td>
<td></td>
</tr>
<tr>
<td>Parietal</td>
<td></td>
<td>265 (6.5)</td>
<td></td>
</tr>
<tr>
<td>Parieto-occipital</td>
<td></td>
<td>11 (0.3)</td>
<td></td>
</tr>
<tr>
<td>Occipital</td>
<td></td>
<td>65 (1.6)</td>
<td></td>
</tr>
<tr>
<td>Parieto-temporal</td>
<td></td>
<td>1 (0.0)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td>1471 (35.9)</td>
<td></td>
</tr>
<tr>
<td>Size of defect (cm²)</td>
<td>100 (48.2)</td>
<td>1.5 – 517.43</td>
<td></td>
</tr>
<tr>
<td>Follow-up (months)</td>
<td>185 (81.1)</td>
<td>0 - 803</td>
<td></td>
</tr>
<tr>
<td>Dropouts</td>
<td>218 (95.6)</td>
<td>247</td>
<td></td>
</tr>
</tbody>
</table>
Of 228 included articles, 118 (51.8%) reported on esthetic outcome after cranioplasty. Eighteen were assessed using a grading system, of which 10 used a custom-made questionnaire including a grading system\textsuperscript{43-52}, 3 studies used the Visual Analog Cosmesis Scale\textsuperscript{53-55}, 2 the cranial index of symmetry\textsuperscript{26,27}, and 2 the Odom criteria\textsuperscript{56,57}. Rotaru et al. used a 3D-reconstructed CT examination to determine esthetic outcome\textsuperscript{20}. In 70 (30.7%) studies an esthetic outcome was mentioned but was subjective as no further measure of evaluation was reported. Thirty-five articles reported esthetic outcome as defined by the patient, 5 as reported by relatives, whereas 14 were assessed by the clinician, and 14 were based on the CT results, of which only 3 were objectively graded. Twelve of these reported on the esthetic outcome as judged by both the patient and the clinician.

Five (2.2%) articles reported QoL after cranioplasty\textsuperscript{12,46,52,55,58}. Manrique et al. and Lindner et al. used the specific University of Washington Quality of Life scale and the generic short-form-36 scale, respectively\textsuperscript{12,58}.

**Characteristics of included patients**

Indications for a cranioplasty were listed in 209 studies, consisting mostly of trauma (n=3352), cerebrovascular (n=2100), tumor (n=1365), or infection (n=222) (Table 1). Two thousand seven hundred twenty patients underwent unilateral, 101 patients bilateral, and 211 patients bifrontal cranioplasties. The affected cranial bone was mentioned in 116 studies (50.9%). The surface area of the defect was mentioned in 110 studies with a mean of 82.6 cm\textsupersquared{} and ranging between 1.5 cm\textsupersquared{} and 517.4 cm\textsupersquared{}. Based on available data from 184 studies comprising 6917 patients, 4191 (60.6%) of them were male. In 200 (87.7%) studies the age was reported and ranged from 0 to 90 years, the mean age was 36.0 years old. Comorbidities were reported in 32 (14.0%) studies. Ten studies mentioned smoking habits.
Surgical characteristics

In 94 studies, the time interval between decompressive craniectomy and cranioplasty was reported, ranging from 0 until 336 months, with a mean of 11.4 months. The use of antibiotics was described in 75 studies, of which some used a combination of antibiotics before, during, and/or after surgery. Seventy studies reported the use of a drain. In 26 papers involvement of the frontal sinus was described. Operation time, as reported in 44 studies, varied between 30 minutes and 544 minutes, with a mean of 146.0 minutes (Table 2).

Table 2: Surgery-specific characteristics of the included cranioplasties (n = 10,346)

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Mentioned in study (%)</th>
<th>Total (%)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>CP material</td>
<td>10346</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Autologous bone</td>
<td>65 (28.5)</td>
<td>3335 (32.2)</td>
<td></td>
</tr>
<tr>
<td>PMMA</td>
<td>60 (26.3)</td>
<td>1644 (15.9)</td>
<td></td>
</tr>
<tr>
<td>Titanium</td>
<td>52 (22.8)</td>
<td>1829 (17.7)</td>
<td></td>
</tr>
<tr>
<td>PEEK</td>
<td>20 (8.8)</td>
<td>250 (2.4)</td>
<td></td>
</tr>
<tr>
<td>Hydroxyapatite</td>
<td>23 (10.1)</td>
<td>905 (8.7)</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>58 (25.4)</td>
<td>2383 (23.0)</td>
<td></td>
</tr>
<tr>
<td>Antibiotic</td>
<td>75 (32.9)</td>
<td>3593</td>
<td></td>
</tr>
<tr>
<td>Preoperative</td>
<td>27 (11.8)</td>
<td>1663 (46.3)</td>
<td></td>
</tr>
<tr>
<td>Peri-operative</td>
<td>42 (18.4)</td>
<td>2362 (65.7)</td>
<td></td>
</tr>
<tr>
<td>Post-operative</td>
<td>50 (21.9)</td>
<td>1737 (48.3)</td>
<td></td>
</tr>
<tr>
<td>Drain</td>
<td>70 (30.7)</td>
<td>2303 / 3207(71.8)</td>
<td></td>
</tr>
<tr>
<td>Involvement of frontal sinus</td>
<td>26 (11.4)</td>
<td>198 / 882 (22.4)</td>
<td></td>
</tr>
<tr>
<td>Operation time (min)</td>
<td>44 (19.3)</td>
<td></td>
<td>30 - 809</td>
</tr>
<tr>
<td>Timing CP after DC (months)</td>
<td>94 (41.2)</td>
<td></td>
<td>0 - 336</td>
</tr>
<tr>
<td>Manufacturing method</td>
<td>187 (82.0)</td>
<td>7800</td>
<td></td>
</tr>
<tr>
<td>Molding</td>
<td>20 (8.8)</td>
<td>560 (7.2)</td>
<td></td>
</tr>
<tr>
<td>No molding</td>
<td>113 (49.6)</td>
<td>5856 (75.1)</td>
<td></td>
</tr>
<tr>
<td>3D printing</td>
<td>6 (2.6)</td>
<td>125 (1.6)</td>
<td></td>
</tr>
<tr>
<td>3D molding</td>
<td>20 (8.8)</td>
<td>454 (5.8)</td>
<td></td>
</tr>
<tr>
<td>CAD/CAM</td>
<td>24 (10.5)</td>
<td>452 (5.8)</td>
<td></td>
</tr>
<tr>
<td>Punch</td>
<td>4 (1.8)</td>
<td>353 (4.5)</td>
<td></td>
</tr>
</tbody>
</table>

CP: cranioplasty
PEEK: poly(ether ether ketone)
PMMA: poly(methyl methacrylate)
DC: decompressive craniectomy
CAD/CAM: computer assisted design / computer assisted manufacturing
Methodological quality
Overall, the included studies were of low quality. Risk of selection bias appeared to be high in 97 (42.5%) of the non-randomized studies (n=226), mainly due to not reporting the selection criteria of the included patients (Table 3). In the 2 randomized control trials, patients were blinded for the material used and the studies were imperfect regarding blinding of the care provider and outcome assessor. Furthermore, the groups were relatively small due to the assumed large variability in infection rates per material, resulting in a skewed power.

<table>
<thead>
<tr>
<th>Quality Question</th>
<th>Yes (N)</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clear definition of study population?</td>
<td>226</td>
<td>100</td>
</tr>
<tr>
<td>Exclusion of selection bias?</td>
<td>130</td>
<td>57.5</td>
</tr>
<tr>
<td>Clear definition of results?</td>
<td>26</td>
<td>11.5</td>
</tr>
<tr>
<td>Clear method to determine results?</td>
<td>13</td>
<td>5.8</td>
</tr>
<tr>
<td>Outcome determined blind from the intervention?</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Affects this the evaluation of the outcome?</td>
<td>226</td>
<td>100</td>
</tr>
<tr>
<td>Follow-up long enough?</td>
<td>79</td>
<td>35.0</td>
</tr>
<tr>
<td>Selective lost to follow up excluded?</td>
<td>197</td>
<td>87.2</td>
</tr>
<tr>
<td>Are confounders described?</td>
<td>10</td>
<td>4.4</td>
</tr>
<tr>
<td>Are the results corrected for confounders? (multi-variate analysis)</td>
<td>10</td>
<td>4.4</td>
</tr>
</tbody>
</table>

Primary outcome measures
None of the outcome measures could be pooled due to clinical heterogeneity, rendering meta-analysis impossible. The overall reported infection rate was 5.6% across all cranioplasty materials used. Autologous cranioplasties showed an infection rate of 6.9%, significantly greater than the combined alloplastic materials (overall: 5.0%; RD = 0.019 [95% CI 0.009-0.030]; NNT = 53 [95% CI 34-116]; RR = 0.73 [95% CI 0.62-0.86]). The lowest infection rate was observed in HA (overall: 3.3%; range: 0-58.8%). The highest infection rate was reported for PMMA (overall: 7.8%; range: 0-50%). Of the 104 studies reporting at least one infection of the cranioplasty (total infected cranioplasties n = 550), 27 included bacteriologic culturing. *Staphylococci* were the most detected infecting agent, causing infection in 90.7% of infected cranioplasties reporting bacterial culture. Specifically, 71.1% tested positive for *Staphylococcus aureus*, including methicillin-resistant *S. aureus* (28.9%) and methicillin-sensitive *S. aureus* (4.1%), 4.1% for *Propionibacterium acnes*, 2.1% for *S. epidermidis*, and 24.7% tested positive for a different bacterial strain. Of these, 16 infected cranioplasties reported multiple strains of bacteria.
Resorption rates were reported in 117 studies. Resorption occurred mostly in autologous grafts, where it was reported in 42 studies and ranged from 0 to 100% with an overall resorption rate of 11.3%.

Cranioplasty removal rate was stated in 194 studies. The lowest graft removal rate was reported for HA (overall: 2.5%). The greatest removal rate was reported for autologous cranioplasties (overall: 10.4%). This was significantly greater than that of the combined alloplastic materials (overall: 5.1%; RD = 0.052 [95% CI 0.039-0.066]; NNT = 19 (95% CI 15-25); RR = 0.50 [95% CI 0.42-0.58]). Overall, removal was required in 6.6% of the cranioplasties in all studies reporting removals.

Other complications
Complications after cranioplasty were reported in 220 studies, with a total complication rate of 18.9%. Hematoma (1.9%), cerebrospinal fluid leak (1.4%), and wound dehiscence (1.1%) occurred most frequently after infection (5.6%) and bone resorption (5.2%) (Table 4).

Autologous bone showed the highest complication rate at 35.7%. HA showed the lowest complication rate at 10.5%. The greatest complication rate was reported by Lee et al., with 135%, as there were multiple complications (total n = 19) per patient after 14 cranioplasties, although it was unclear how these complications were distributed amongst the patients. The lowest complication rate was reported by Liu et al., who stated that all 598 patients did not show any complications following 611 cranioplasties. Timing of complications after cranioplasty was reported in 72 studies, ranging from immediately to 9 years after decompressive craniectomy.

Treatment policy after complications
Of the 220 studies reporting complications, 122 mentioned a treatment plan. Removal of the cranioplasty was reported in 6.6% of cases, followed by 2.2% surgeries, and 1.6% cases of expectative policy. Other policies, including antibiotic treatment and wound debridement, were performed in 0.5% of cases (Table 4).
Autologous bone is inferior to alloplastic cranioplasties

<table>
<thead>
<tr>
<th>Complications</th>
<th>Total n (%)</th>
<th>PEEK n (%)</th>
<th>PMMA n (%)</th>
<th>Titanium n (%)</th>
<th>Autologous n (%)</th>
<th>HA n (%)</th>
<th>Other n (%)</th>
<th>Unknown n (%)</th>
</tr>
</thead>
<tbody>
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<td>Hematoma</td>
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<th>Titanium n (%)</th>
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PEEK: poly(ether ether ketone)
PMMA: poly(methyl methacrylate)
HA: hydroxyapatite

Neurological function
The GCS and GOS scores varied from 5 to 15 and 1 to 5 respectively. Twenty-two of 44 studies reported the neurological outcome in a subjective manner. Both numerical and subjective studies showed high heterogeneity ranging from ‘Nine of 12 (75%) patients with neurological disability showed some improvement in neurological status’ to the GOS ‘improved significantly after the cranioplasty’.
Costs
Twenty-one studies reported costs, ranging from implant cost to total medical expenses. PMMA implants were less expensive than PEEK and titanium implants. The least-expensive PMMA implant was 35 GBP\(^64\), the most expensive PMMA implant was 1300 USD after 3D printing\(^65\). The costs of PEEK ranged from 5000 USD\(^66\) to 20,522 USD\(^67\). Titanium cranioplasties cost between 2000 GBP\(^64\) and 5050 EUR\(^55\). Total surgery costs for PSIs of PEEK and titanium were reported to be 15,532 EUR (of which 10,000 EUR for the implant), compared with 10,849 EUR for autologous replacement\(^68\). Gilardino et al.\(^69\) reported a total cost of 28,560 USD for treatment with PEEK, whereas autologous treatment costs were 25,797 USD.

Esthetic outcome
Most patients were satisfied or highly satisfied with the eventual esthetic outcome. All of the studies reporting both patient and clinician satisfaction showed they were in agreement.

Quality of Life
Five studies reporting the QoL showed an improvement after cranioplasty. Manrique et al.\(^58\) reported that 3 of 4 patients had returned to a similar state as before the skull defect, whereas 1 patient reported dissatisfaction with his appearance and had an overall fair QoL as measured with the Head and Neck Outcome Questionnaire from the University of Washington. Lindner et al.\(^12\) used the short-form-36 questionnaire to evaluate the subjective QoL and stated patients treated with a titanium or HA cranioplasty were “more satisfied at the end of the study than at the beginning”. Moser et al.\(^52\) described that 82.4% of the patients had an improved QoL postoperatively, based on 10 easy-to-understand questions in the German language. Cabraja et al.\(^55\) showed all patients had a “considerable improvement in their QoL following calvarial reconstruction” and would “undergo cranioplasty again”. Also Kamyszek et al.\(^46\) noted a “clear positive trend” in QoL and 85% of patients “would undergo the procedure again”.


DISCUSSION

This systematic review shows that cranioplasties are associated with a high complication rate, particularly when using autologous bone, mainly because of the high infection and resorption rates and subsequent graft removal.

Resorption occurred most frequently in autologous bone, which is inherent to the tissue and may compromise the structural integrity. Resorption in allografts is limited to the interface between implant and surrounding bone and may therefore be less likely to occur. Other complication rates in autologous bone cranioplasties are more similar to, for example, HA, which is the main mineral constituent of bone. PEEK is custom made preoperatively, requires less surgical time, and has no burrs that require removal.

To date, 228 studies on the safety of cranioplasties are available, published during a 65-year span. However, a large variety exists in reported primary and secondary outcomes, and their definitions, as well as the protocols applied for cranioplasties, which makes meta-analysis futile. Meta-analyses in some reviews were conducted with heterogeneous studies, whereas other reviews largely focused on a subjective analysis of the most commonly used materials. Corliss et al. included 48 studies (n=5346 patients) and related the way of storage (abdominal pocket or cryopreservation) of autologous bone flaps for cranioplasties to survival rates. They found a total infection rate of 7.32% (n=2937) in the cryopreservation group versus 7.08% (n=527) in the abdominal pocket group. Resorption rate in 19 studies was 9.66% (n=1826) in the cryopreservation group and 7.69% (n=341) in the abdominal pocket group. Malcolm et al. reported similar infection rates, but the materials used for cranioplasty were not reported. Punchak et al. found an infection rate of 6% in a meta-analysis of 15 studies applying 183 PEEK cranioplasties. These reviews had a limited scope, disregarding putative confounders such as patient population, comorbidities, defect location and size, time between decompressive craniectomy and cranioplasty, material, antibiotics usage, frontal sinus involvement, or drain placement.
Beside the clinical results evaluated in this review, physical properties of the various materials may also influence procedure safety. A better understanding of these properties is vital in the development of future materials for cranioplasty. Of the products commonly used, titanium has a good biocompatibility, shows resistance to infection, and appears to be mechanically stable\(^{11,72}\). However, titanium is expensive. Furthermore, it is radiopaque and easily conducts heat and cold\(^{10}\). PMMA is widely used for cranioplasty, relatively inexpensive, light in weight, easy to use, and radiolucent. Nonetheless, PMMA is associated with disadvantages, such as a greater infection rate, and it does not facilitate bone ingrowth and revascularization\(^{10}\). In addition, the residual monomer is considered to be toxic\(^{73-76}\). In this systematic review, an overall infection rate of 7.8% was noted. PMMA is mostly formed intraoperative, without polishing. Bacterial adhesion and biofilm deposition is stimulated by irregularities, which could contribute to an increased infection rate\(^{77}\). HA is an established material for cranioplasty. It is biocompatible and similar to the mineral structures of human bone. This allows the implant to be broken down over time and replaced by newly formed bone. However, before remodeling has taken place the HA is brittle and vulnerable to fracture. It therefore seems most suitable for small defects\(^{78}\). PEEK is a relatively new material for cranioplasties. It has high structural stability and can be sterilized using various methods without deformation. However, PEEK has some disadvantages: the material itself is costly and it has no bioactive potential\(^{71,79}\).

Combining multiple existing materials allowed for the development of new cranioplasty products, for example, a titanium mesh used in combination with different types of bone cement\(^{10}\). In addition to commonly used materials, other new materials for cranioplasty are being developed, such as bioactive fiber-reinforced composite implant, hard tissue replacement polymer and carbon fiber reinforced polymer\(^{80-82}\). Most of these materials, however, have merely been evaluated in preliminary studies with small patient groups.

Resorption rates up to 50%\(^{83}\) have been observed for autologous cranial reconstructions, and there is evidence suggesting that younger patients may have significantly greater resorption rates. Greater metabolic activity in younger patients could lead to quicker resorption, but the exact mechanism responsible for this complication is unclear\(^{84}\). This phenomenon suggests that young patients may be better served by an immediate alloplastic reconstruction.
Autologous bone is inferior to alloplastic cranioplasties

Study limitations
Virtually all currently available evidence on the safety of cranioplasty materials is retrospective, limiting the amount of relevant data available for review.

Reliability of the reported infection rates in the included studies was questionable, because a significant number of studies synonymized infection and removal of the cranioplasty after infection or did not specify their definition of infection. Malcolm et al. already noted this wide range of definitions for infection. This was also true for the definition of resorption. Neurologic functioning and aesthetic outcome were often reported subjectively and were sometimes included as a complication.

HA likely was used in smaller and safer located defects resulting in skewed conclusions. It may also be prevalent in pediatric situations, to accommodate a growing skull; naturally, these patients have a greater capacity for recovery than elderly patients. This review did not correct for these parameters, and future studies should aim to verify these results.

In some studies, the amount of cranioplasties, whether it was unilateral or not, and the affected cranial bone was not reported. In these cases, we assumed the number of patients was equal to the amount of cranioplasties.

A number of the non-primary outcome complications could not be attributed to a material as only studies that did not report the primary outcomes per material were excluded.

CONCLUSION

Implications for practice
This systematic review of a substantial body of evidence offers insufficiently strong evidence to conduct a meta-analysis or support the use of any material over another for cranioplasty. However, available evidence does show a significantly lower removal rate for alloplastic materials for cranioplasty than for autologous bone. Hence, autologous bone is dissuaded for cranioplasty after decompressive craniectomy.
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Implications for research
Based on this review, well-conducted prospective studies are warranted to generate convincing evidence on which allograft material is preferable for cranioplasty. Uniform reporting guidelines, including likely confounders, will help improve the quality of the conduct and reporting of studies in this realm and allow proper comparison between studies. This may lead to standardization of surgical protocols and development of better materials for cranioplasty and ultimately an evidence-based choice of allografts for patients who require cranioplasty. These guidelines should, at a minimum, provide clear definitions of infection and resorption, the two most reported complications in cranioplasties.
Autologous bone is inferior to alloplastic cranioplasties

REFERENCES


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Autologous bone is inferior to alloplastic cranioplasties


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Supplemental Digital Content

S.1: Search terms

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S.2: Included studies in this systematic review

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