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Autologous Cranioplasty is Associated with Increased Reoperation Rate: A Systematic Review and Meta-Analysis

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■ OBJECTIVE: Consensus regarding selection of synthetic versus autologous flap reimplantation for cranioplasty after decompressive craniectomy has not been reached and the multiple factors considered for each patient make comparative analysis challenging. This study examines the association between choice of material and related complications.

■ METHODS: A systematic literature review and meta-analysis were performed using PubMed for articles reporting delayed cranioplasty after decompressive craniectomy using a cohort design comparing autologous bone and synthetic implants. Extracted data included implant material and incidence of infection, reoperations related to implant, wound complications, and resorption.

■ RESULTS: One randomized controlled trial and 11 cohort studies were included for a total of 1586 implants (950 bone, 636 synthetic). Autologous implants had significantly more reoperations than did synthetic implants ($n = 1586$ implants; odds ratio [OR], 1.91; 95% confidence interval [CI], 1.40–2.61). Reoperations were most often because of resorption (54%, $n = 159/295$) followed by infection (41%, $n = 121/295$). The pooled incidence of resorption in autologous implants was 20% ($n = 159/791$). Among the other outcomes, there was no significant difference for infections ($n = 1586$; OR, 1.24; CI, 0.82–1.88) or wound complications ($n = 678$; OR, 0.56; CI, 0.22–1.45). For the trauma subpopulation, there was no significant difference in infection rate with either material ($n = 197$; OR, 1.89; CI; 0.59–6.09).

■ CONCLUSIONS: Autologous implants had significantly more reoperations primarily because if the intrinsic risk of resorption (level of evidence 3b).

INTRODUCTION

Cranioplasty after decompressive craniectomy is a routine neurosurgical procedure to restore cosmesis, provide cerebral protection, facilitate neurologic rehabilitation, and improve neurologic outcome.[1] Cranioplasty, although considered routine by many, can be associated with significant morbidity.[2-6] The choice of implant material has received considerable attention as a potential modifiable risk factor.[7-9] This choice is typically at the discretion of the operating surgeon or institution. In cases of fragmented or grossly infected bone, the use of synthetic implant seems obvious, but more often the choice is one of cost or convenience.

The purpose of this study was to 1) assess for reported associations between implant material and subsequent complications and 2) catalogue other risk factors for these complications. To answer these questions, a review of the literature and meta-analysis was performed to examine the complications after cranioplasty using either autologous bone or synthetic implants.
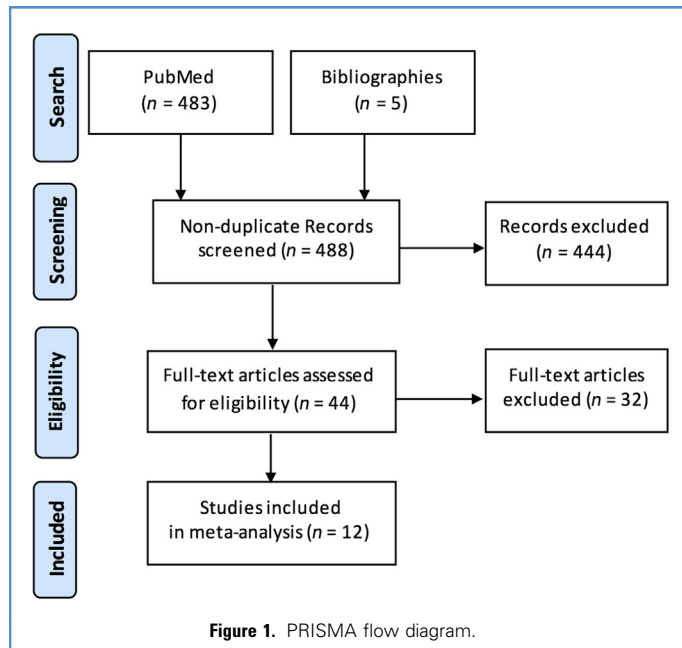
METHODS

Search

A systematic review of the literature adherent to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines was performed for published articles reporting on complications related to cranioplasty material.[10] The PubMed/MEDLINE database was searched for articles on cranioplasty procedures that compared both bone versus synthetic materials using the query: "cranioplasty AND (material OR ((autologous OR bone OR allograft) AND (synthetic OR bone-substitute OR polymethylmethacrylate OR PMMA OR titanium OR acrylic OR hydroxyapatite)))." The search was restricted to original clinical studies published between January 2000 and April 2018. From preliminary reading, studies preceding this period tended to use nonstandard techniques or materials no longer in common use, and so the decision was made to exclude older studies. Thorough bibliographic searches of qualifying articles and relevant medical journals were also performed to identify additional articles for inclusion.

Selection Criteria

Articles reporting on complications after cranioplasty using either autologous bone

Figure 1. PRISMA flow diagram.

was used to quantify heterogeneity (0% = no heterogeneity; 100% = maximal heterogeneity).[33] The χ^2 test was used to evaluate significant differences between subgroups. P values < 0.05 were considered statistically significant.

Assessment of Bias

The study quality of individual articles was determined by using the Oxford Center for Evidence-Based Medicine guidelines.[34] Risk of bias was assessed by the Newcastle-Ottawa Scale, which is a 3-category, 9-point scale assessing cohort selection, comparability, and outcome, with a higher score indicating higher quality.[35]

RESULTS

Literature review results are shown in the PRISMA flow diagram (**Figure 1**). The search identified 483 nonduplicate studies spanning January 1, 2000 to April 30, 2018. Five additional studies were identified from bibliographies.[31,36-39]

The final 12 included studies represented 1586 cranioplasty procedures with a clear preference toward use of a patient's own bone (950 bone, 636 synthetic). **Table 1** lists individual study characteristics. Included were 1 randomized controlled trial (Oxford Center for Evidence-Based Medicine evidence level 1) and 11 cohort studies (level 3b). Indications for initial craniectomy included trauma (most common), ischemic or hemorrhagic stroke, infection, and tumors. **Table 2** summarizes these characteristics across studies.

A variety of synthetic implants were used. Two of the most common were titanium and polymethylmethacrylate. Various other combinations of prefabricated or intraoperative molded implants were made from polyethylene, polyetheretherketone, hydroxyapatite, and various other acrylics and ceramics. Autologous bone implants underwent a variety of handling protocols, most commonly soaking in betadine and frozen storage; however, a few studies autoclaved the bone before reimplantation. One study used a method called Tutoplast processing for autologous bone, which involves a combination of sonication to remove fat, hydrogen peroxide to kill viruses, acetone to dry out prions, and gamma radiation.[32]

or synthetic implant were included in the analyses. With a large body of literature mentioning material choice, only studies specifically designed to compare material choice were included, (e.g., clinical trials and cohort studies). Case series that merely mention material choice were excluded. Further, included studies must have had at least 20 patients with at least 3 months follow-up. Technical notes, letters, and editorials were excluded. Reviews were also excluded; however, referenced articles were thoroughly screened for possible inclusion.[2,7,11] Studies that involved animals, included noncalvarial or maxillofacial procedures, or focused exclusively on the pediatric population were excluded.[12-14] Studies were excluded if more than a quarter of patients underwent nondecompressive single-stage craniectomy (e.g., for resection of meningioma).[15,16] The search results were independently screened by 2 authors (J.M. and Z.M.); disagreements were resolved by consensus. The following studies were excluded: split calvarial or rib grafts,[17-22] comparison only among different synthetic options,[23-27] reporting data not suitable for analysis,[3,28] non-English language,[29] focused only on epidural fluid collections,[30] or a significant portion of patients with previous cranioplasty procedures.

Data Extraction

The following data were extracted from each article, if reported: number of patients, indication for initial craniectomy, number of autologous bone implants, number of synthetic implants, type of synthetic material, infection, reoperations, wound complications, clinically significant bone resorption (aseptic necrosis), and any risk factors identified. If an implant included primarily bone but was supplemented with allograft, it was considered an autograft.[31] Nondestructive processing of autologous bone was ignored (e.g., autoclave,[31] fat sonication[32]).

Statistical Analysis

Data were analyzed using Review Manager 5.3.5 (The Cochrane Collaboration). For each complication, odds ratios (OR) and 95% confidence intervals (CI)s were calculated to estimate the odds of each complication for autologous bone implant (i.e., OR <1 indicates bone is associated with decreased complication rate, whereas synthetic material is associated with an increased rate). Odds ratios were pooled using the Mantel-Haenszel method with a fixed-effects model, except where the χ^2 test indicated significant heterogeneity among studies, in which case a random-effects model was used. The I^2 metric

Table 1. Characteristics of Included Studies Reporting Complications Related to Choice of Cranioplasty Material

Reference	Design	Level of Evidence	Quality	Indication for Craniectomy	Implants		Synthetic Material	Complication			
					Bone	Synthetic		Infection	Reoperations	Wound Complication	Bone Resorption
Kriegel et al., 2007[32]	Cohort	3b	6	MCA infarct, SAH, infection, trauma, ICH, tumor	18	30	PMMA	Y	Y	Y	Y
Cheng et al., 2008[40]	Cohort	3b	5	Trauma, nontrauma	52	32	PMMA	Y	Y		
Lee et al., 2009[41]	Cohort	3b	9	Trauma, infarction, ICH, SAH	91	40	PMMA	Y	Y	Y	
Im et al., 2012[41]	Cohort	3b	7	Trauma, vascular, tumor	83	48	PMMA, PE, bone cement	Y	Y	Y	Y
Bobinski 2013[42]	Cohort	3b	9	Trauma	30	19	PMMA	Y	Y	Y	Y
Lethaus et al., 2014[43]	Cohort	3b	8	Trauma, CVA, tumor, infection, hydrocephalus, epilepsy	16	17	Ti, PEEK	Y	Y		Y
Iaccarino et al., 2015[44]	Cohort	3b	7	Trauma, stroke, SAH, tumor, infection	31	65	PMMA, PEEK, HA	Y	Y		Y
Piitulainen et al., 2015[45]	Cohort	3b	9	Trauma, tumor, infection, hemorrhagic, ischemic	20	80	PMMA, PE, HA, bioactive fiber-reinforced composite	Y	Y	Y	Y
Schwarz et al., 2016[9]	Cohort	3b	7	Trauma, infarction, extra-axial bleeding, SAH, ICH, tumor	503	128	PEEK, Ti, ceramic	Y	Y		Y
Honeybul et al., 2017[8]	RCT	1	9	Trauma, ischemic, hemorrhagic, tumor	32	32	Ti	Y	Y		Y
Kim et al., 2017[46]	Cohort	3b	9	Trauma, ischemic, hemorrhagic, tumor, infection	30	97	PMMA	Y	Y	Y	Y
Moles et al., 2018[47]	Cohort	3b	9	Trauma, intracranial hypertension, ischemic, SAH, infection, tumor	44	48	HA	Y	Y	Y	Y
				Totals	950	636		12	12	7	10
					1586						

MCA, middle cerebral artery; SAH, subarachnoid hemorrhage; ICH, intracerebral hemorrhage; PMMA, polymethylmethacrylate; Y, yes; PE, porous polyethylene; CVA, cerebrovascular accident; Ti, titanium; PEEK, polyetheretherketone; HA, hydroxyapatite; RCT, randomized controlled trial.

Table 2. Summary Characteristics of Included Studies

	n (%)
Materials	
Bone	950 (60)
Synthetic	636 (40)
Total	1586
Study design	
Randomized controlled trial	1
Cohort	11
Total	12
Indication for craniectomy	
Trauma	656 (41)
Vascular	599 (38)
Tumor	61 (3.8)
Infection	54 (3.4)
Nontrauma, unspecified	24 (1.5)
Unspecified	5 (0.3)

The investigators compared this processing protocol with acrylic implants. One study used a subcutaneous abdominal pocket.[47]

The study quality averaged 7.8 of a possible 9 points on the Newcastle-Ottawa Scale (range, 5–9; **Table 1**). Seven studies had some level of cohort matching to reduce the risk of selection bias (level 3b).[8,41-43,45-47]

Infections

All studies reported infection rates. Infection was defined variably across studies but in all cases required clinical symptoms such as persistent fever, meningismus, positive systemic or wound cultures, or purulent wound discharge. Although most studies classified infection as requiring reoperation for debridement and washout, some included cases that resolved with antibiotics alone.[48]

Figure 2 shows the meta-analysis for odds of developing infection. The pooled rate of infection was 8.0% (n = 76/950) for autologous bone and 7.1% (n = 45/636) for synthetic implants (overall, 7.6%; n = 121/1586). There was a nonsignificant trend toward infection with bone (n = 1586; OR, 1.24; CI, 0.82–1.88; P = 0.30). There was no significant heterogeneity, so a fixed-effects model was used ($I^2 = 32\%$; P = 0.14).

Five of the studies[8,32,40,42,46] included only patients with trauma or reported data separately for patients with trauma, which allowed for a subgroup analysis shown in **Figure 3**. The rate of infection was 6.6% (n = 13/197) and there was no difference in odds of infection for different materials (n = 197; OR, 1.89; CI, 0.59–6.09; P = 0.28). No other subpopulation (e.g., vascular) had enough data for subgroup analysis.

Only 1 study[49] identified poor preoperative neurologic status as an independent risk factor for infection (Glasgow Outcome Scale score 2–3; hazard ratio, 5.2; CI, 1.1–25.2; P = 0.04).

Reoperations

All studies reported reoperation rates. Among all reoperations (n = 295), the most common cause was resorption (n = 159/295, 54%) followed by infection (n = 121/295, 41%). Reoperations for hematoma evacuations or reoperation to treat the primary disease process (e.g., aneurysm clipping) were not considered related to cranioplasty material and thus not counted.[32,41,43]

Figure 4 shows the meta-analysis for odds of reoperation. The pooled rate of reoperations was 23.2% (n = 221/950) for autologous bone and 11.6% (n = 74/636) for synthetic implants (overall, 18.6%; n = 295/1586). Across all studies, there was a significant increase in odds of reoperation with bone (n = 1586; OR, 1.91; CI, 1.40–2.61; P < 0.0001). There was no significant heterogeneity, so a fixed-effects model was used ($I^2 = 27\%$; P = 0.18).

No study identified specific risk factors for reoperation.

Wound Complications

Seven studies reported wound complications. Examples of wound complications included aseptic wound dehiscence,[32,41] dislodged implant,[42] and unspecified wound revision.[49]

Figure 5 shows the meta-analysis for odds of developing wound complications. The pooled rate of wound complications was 1.3% (n = 4/316) for autologous bone and 2.8% (n = 10/362) for synthetic implants (overall 2.1%; n = 14/678). Although bone had fewer wound complications, this did not reach significance (n = 678; OR, 0.56; CI, 0.22–1.45; P = 0.23). There was no significant

heterogeneity, so a fixed-effects model was used ($I^2 = 3\%$; P = 0.40).

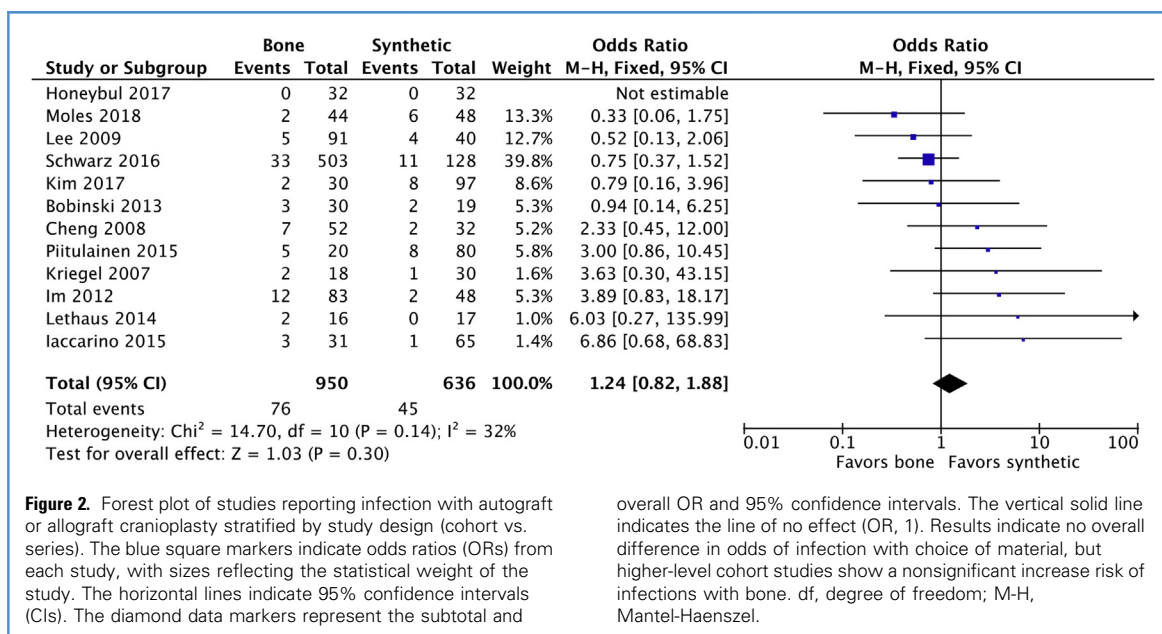No study identified risk factors for wound complications.

Bone Resorption

Ten studies reported resorption rates (**Table 3**). In general, a minimum of 6 months of follow-up are necessary to appreciate resorption of autologous bone, and most studies in this analysis considered 1 year to be adequate. The definition of resorption varied among studies, but nearly all considered only clinically significant resorption that would necessitate reoperation, such as palpable defects or implant loosening. The pooled rate of resorption for autologous grafts was 20% (n = 159/791).

Two studies identified young age as a risk factor although they each considered it differently: OR, 0.97 (CI, 0.95–0.98) risk reduction with each year of age,[9] or alternatively age <20 years with P = 0.033 (no OR reported).[32] Fragmented bone graft into 2 pieces (OR, 3.71; CI, 1.89–7.29), fragmentation into >2 pieces (OR, 22.01; CI, 9.43–51.61), or the presence of a ventriculoperitoneal shunt at time of cranioplasty (OR, 1.73; CI, 1.02–2.92) also increased the risk of resorption.[9] Tissue processing may have been a factor. The highest rate of bone resorption (39% of patients with 6 months follow-up) was observed in the 1 study using Tutoplast (Tutogen Medical GmbH, Neunkirchen am Brand, Germany) processing of autogenous bone.[32] Similarly, another study[46] that used significant processing (autoclaving, hydrogen peroxide, and gas plasma) reached 60% (n = 18/30) resorption, although only 13% (n = 4/30) were significant enough to warrant reoperation.

DISCUSSION

This analysis shows that the use of autologous bone for cranioplasty is associated with significantly increased odds of reoperation compared with synthetic grafts, likely because of infection or resorption. Although synthetic materials often require increased upfront cost, the potential for additional cost of reoperation after autologous implantation should be considered, especially in high-risk patients (i.e., poor neurologic status, fragmented bone graft, or a preexisting shunt). With more than a

Figure 2. Forest plot of studies reporting infection with autograft or allograft cranioplasty stratified by study design (cohort vs. series). The blue square markers indicate odds ratios (ORs) from each study, with sizes reflecting the statistical weight of the study. The horizontal lines indicate 95% confidence intervals (CIs). The diamond data markers represent the subtotal and overall OR and 95% confidence intervals. The vertical solid line indicates the line of no effect (OR, 1). Results indicate no overall difference in odds of infection with choice of material, but higher-level cohort studies show a nonsignificant increase risk of infections with bone. df, degree of freedom; M-H, Mantel-Haenszel.

thousand procedures spanning a decade of recent practice, this is the largest, most rigorous study to date on the topic. Furthermore, it is the first study to examine reoperations as a whole, which affects patient outcomes and health care costs regardless of indication. Despite it being a widely discussed topic, only 1 small randomized controlled trial has been reported, which showed no difference against titanium.[8,50] This study suggests that the choice of material may reduce complications that would otherwise set back overall recovery and rehabilitation.
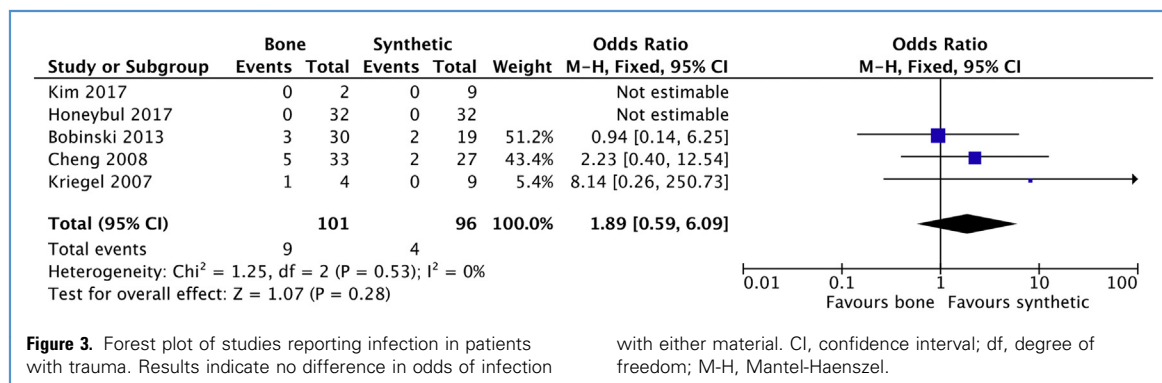
Infection

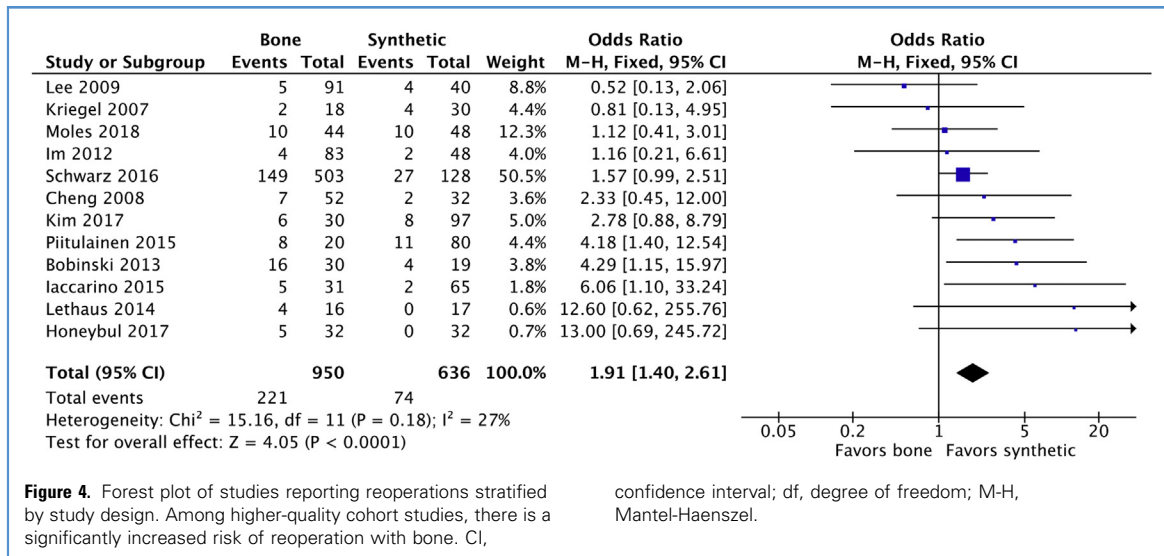Infection was the most commonly reported complication after cranioplasty, with an average reported incidence of 7.6% regardless of material (n = 121/1586). This finding is consistent with the earlier review by Yadla et al.[7] that also examined the relationship between material and infections (8.6%, n = 137/1582). Another recent expanded review[2] catalogued all reported cranioplasty complications and reported a rate of 6.0% (n = 565/9359). It is reasonable to quote an overall expected infection rate between 5% and 10%, which is not trivial given the subsequent steps that are required to address the infection (i.e., reoperation for flap removal, long-term intravenous antibiotics, and reoperation for skull reconstruction with synthetic material).

Autologous bone did not seem to increase infection rates compared with synthetic material in this analysis (OR, 1.24; CI, 0.82−1.88). This finding is consistent with previous reviews.[7] Among cited risk factors, there is a clear consensus in the literature that poor preoperative neurologic status (variously defined) is a significant risk factor for subsequent infection.[31,36,51-54]

In the trauma subpopulation, the incidence of infection after cranioplasty is estimated at 7.4% (n = 172/2318) compared with 5.6% (n = 393/7041) for nontraumatic (e.g., ischemic stroke and hemorrhagic stroke).[2] The question then follows: should the original bone flap be discarded in patients with trauma? According to our study, the answer is likely no, because there was no difference in infections between bone

Figure 3. Forest plot of studies reporting infection in patients with trauma. Results indicate no difference in odds of infection with either material. CI, confidence interval; df, degree of freedom; M-H, Mantel-Haenszel.

Figure 4. Forest plot of studies reporting reoperations stratified by study design. Among higher-quality cohort studies, there is a significantly increased risk of reoperation with bone. CI, confidence interval; df, degree of freedom; M-H, Mantel-Haenszel.

and synthetic implants (OR, 1.89; CI, 0.59–6.09). This finding is, of course, in exclusion of any grossly contaminated bone flap at the time of initial craniectomy. Given the heterogenous nature of these data, prospective controlled trials are needed to investigate this topic further.

Can infections be reduced with improved handling or sterilization of the implant? The answer seems to be no. One study swabbed all bone before storage; those with positive cultures were sterilized by soaking in bacitracin before implantation, whereas those with negative cultures were reimplanted without additional processing.[4] The investigators found no difference among infection rates for sterilized bone, nonsterilized bone, or synthetic flaps. Furthermore, of the 3 positive-culture flaps requiring bacitracin

that resulted in clinical infection, all grew different species from those identified at time of craniectomy. These findings seem to indicate that the source of infection has little to do with preimplantation sterilization and handling. Rather, it may be that aggressive processing and sterilization damage the bone and can lead to resorption, as discussed later.[32,46]

Antibiotic-impregnated synthetics, such as acrylics and polymethylmethacrylate, have shown promise.[55] Two series have reported reduced infection rates using polymethylmethacrylate implants impregnated with vancomycin/tobramycin[56] and erythromycin/colistin.[57]

Reoperations
Autologous bone implants showed a significant risk of reoperation secondary to infection or resorption (OR, 1.91; CI,

1.40–2.61) with little heterogeneity ($I^2 = 27\%$; $P = 0.18$). Although in some cases, infection may be treated with antibiotics alone, a return to the operating room first for explantation, and again later for reimplantation, carries significant risk and cost. When mentioned, all studies discarded the previous autologous implant at reoperation and used a new synthetic implant, which further increases expense. Any cost analysis must take into consideration not just the initial implant and operative procedure but also some estimate of these reoperations.

Wound Complications
The pooled rate of wound complications after cranioplasty was small, and similar in both autologous and synthetic grafts (1.3% autologous vs. 2.8% synthetic). The meta-analysis showed no significant difference
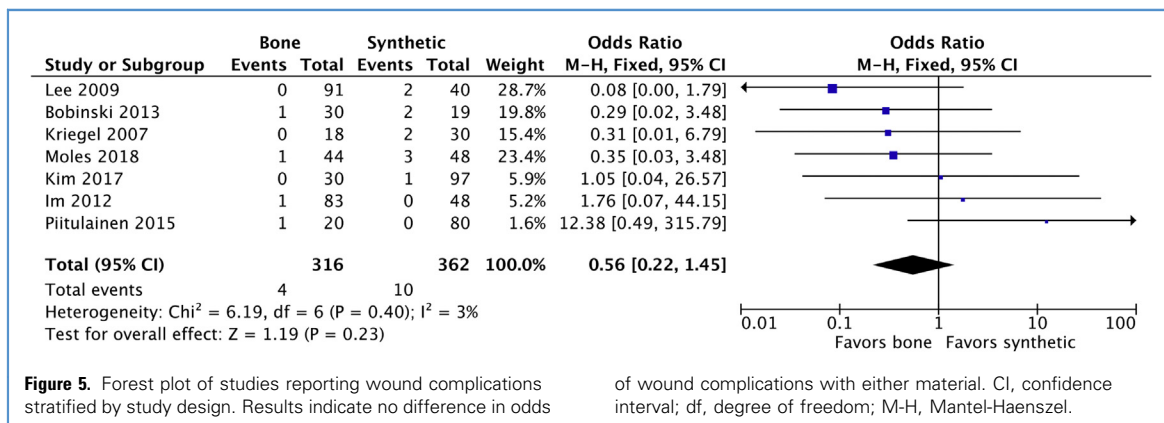

Figure 5. Forest plot of studies reporting wound complications stratified by study design. Results indicate no difference in odds of wound complications with either material. CI, confidence interval; df, degree of freedom; M-H, Mantel-Haenszel.

Table 3. Incidence of Resorption Reported in Each Study and Pooled Estimate

Reference	Cases with Resorption	Cases with Follow-Up	Rate (%)	Risk Factors
Kriegel et al., 2007[32]	7	18	39	Young age
Im et al., 2012[41]	15	77*	19	
Bobinski et al., 2013[42]	6	30	20	
Lethaus et al., 2014[43]	3	16	19	
Iaccarino et al., 2015[44]	2	31	6	
Piitulainen et al., 2015[45]	3	20	15	
Schwarz et al., 2016[9]	108	503	21	Fragmented, young age, ventriculoperitoneal shunt
Honeybul et al., 2017[8]	7	31*	23	
Kim et al., 2017[46]	4	30	13	
Moles et al., 2018[47]	4	35*	11	
Total	159	791	20	

*Number of patients in study with imaging and clinical follow-up appropriate to assess resorption.

in wound complications between use of autologous bone and synthetic implants. Wound complications were relatively rare occurrences and may require higher numbers to better evaluate any difference between groups.

Resorption

Resorption is an often underreported complication, with little more than half the studies included in this analysis providing data and follow-up. Resorption typically takes up to a year to present with symptomatic effects.[9] Most patients do not undergo surveillance neuroimaging unless there are specific concerns, so resorption is usually discovered after a patient develops a cosmetic defect. A recent systematic review estimated the prevalence of resorption to be about 16%,[2] similar to our rate (20%). In addition, the definition of significant resorption varies among studies, ranging from mild translucency on imaging that requires no intervention to complete full-thickness erosion and cosmetic defects. This spectrum has been divided into 2 types: thinning of the bone on imaging or by palpation (type I) versus complete lysis of the inner and outer tabula with loss of cerebral protection requiring revision (type II).[9] In our review, nearly all studies reported only resorption associated with cosmetic or palpable defects (type II). There is some evidence that younger age is a risk factor for resorption, which may

prompt use of synthetic implants in the pediatric population when possible.[9,32,52,58] Serial follow-up imaging to screen for resorption is not recommended; rather, patients should have expectant follow-up and should be advised to seek attention sooner if palpable defects are noted. Most cases can be managed conservatively unless there is significant bone loss or cosmetic defect. Significant processing of bone grafts at the time of cranioplasty should be avoided, because it does not seem to improve infection rates and may worsen resorption rates as a result of microstructural damage.[22,32,46]

Limitations

Several factors potentially bias the findings in this study. First, all but 1 included study were retrospective observational cohorts, and the 1 randomized controlled trial was relatively small (n = 64).[8] With a variety of reasons for decompression, the reason for choosing a material is not controlled and there was a clear preference for reusing a patient's own bone (950 bone vs. 636 synthetic). We recommend that future studies stratify by primary disease (e.g., trauma, ischemic, hemorrhagic, or tumor). Second, complications for all synthetic material types were combined. It is likely that each material has different biomechanical properties that influence infection and wound healing. There are a multitude of synthetic options, but future studies should

consider direct comparison of different materials (e.g., titanium vs. polyetheretherketone vs. acrylic). In 1 randomized controlled trial (n = 52), titanium was associated with higher infection rates compared with hydroxyapatite, but both cohorts had similar reoperation rates.[59] Third, there was a variety of definitions of infection (superficial vs. deep vs. global), resorption (slight vs. significant), and reoperation (explantation vs. supplementation). The nature of a reoperation could not always be discerned; future studies should specify which reoperations involved complete explantation (with delayed cranioplasty) rather than simple cosmetic supplementation or debridement. Future studies should also consider stratifying major and minor complications. Examples of major complications might include infection requiring explantation, resorption requiring replacement, or supplementation for cosmetic defects. Examples of minor complications might include superficial infection treated with antibiotics, debridement, or simple wound revision. Furthermore, some patients may have been considered twice in the same analyses. For example, patients who underwent reoperation with synthetic material after a failed autologous cranioplasty were included in both groups.[15,40,43,60] The incidence of this situation is low enough that

significant bias in this study is unlikely; however, future studies should consider keeping patients within their intent-to-treat assignment to minimize bias. The comparative costs of these implants have not been fully examined.[20] Autologous bone requires long-term storage before implantation, whereas synthetic grafts often come with a steep upfront cost. It is unclear whether the risk of reoperation that goes along with autologous grafts justifies the regular use of synthetic implants.

CONCLUSIONS

There are few well-designed studies reporting cranioplasty outcomes and complications. Infection rates are similar between autologous and synthetic options in both the overall population and the population with trauma. Autologous implants are associated with significantly more reoperations driven primarily by the intrinsic risk of resorption. Future studies should consider randomizing material selection, stratifying patients by primary disease, and directly comparing synthetic materials head to head.

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