Predictors of infection after 754 cranioplasty operations and the value of intraoperative cultures for cryopreserved bone flaps

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OBJECTIVE The authors' aim was to report the largest study on predictors of infection after cranioplasty and to assess the predictive value of intraoperative bone flap cultures before cryopreservation.

METHODS They retrospectively examined all cranioplasties performed between March 2004 and November 2014. Throughout this study period, the standard protocol during initial craniectomy was to obtain a culture swab of the extracted autologous bone flap (ABF)—prior to its placement in cytostorage—to screen for microbial contamination. Two consecutive protocols were employed for the use and interpretation of the intraoperative swab culture results: A) From March 2004 through June 2013, any culture-positive ABF (+ABF) was discarded and a custom synthetic prosthesis was implanted at the time of cranioplasty. B) From July 2013 through November 2014, any ABF with a skin flora organism was not discarded. Instead, cryopreservation was maintained and the +ABF was re-implanted after a 10-minute soak in bacitracin irrigation as well as a 3-minute soak in betadine.

RESULTS Over the 10.75-year period, 754 cranioplasty procedures were performed. The median time from craniectomy to cranioplasty was 123 days. Median follow-up after cranioplasty was 237 days for protocol A and 225 days for protocol B. The overall infection rate after cranioplasty was 6.6% (50 cases) occurring at a median postoperative Day 31. *Staphylococcus* spp. were involved as the causative organisms in 60% of cases.

Culture swabs taken at the time of initial craniectomy were available for 640 ABFs as 114 ABFs were not salvageable. One hundred twenty-six (20%) were culture positive. Eighty-nine +ABFs occurred during protocol A and were discarded in favor of a synthetic prosthesis at the time of cranioplasty, whereas 37 +ABFs occurred under protocol B and were reimplanted at the time of cranioplasty.

Cranioplasty material did not affect the postcranioplasty infection rate. There was no significant difference in the infection rate among sterile ABFs (7%), +ABFs (8%), and synthetic prostheses (5.5%; $p = 0.425$). All 3 +ABF infections under protocol B were caused by organisms that differed from those in the original intraoperative bone culture from the initial craniectomy. A cranioplasty procedure ≤ 14 days after initial craniectomy was the only significant predictor of postcranioplasty infection ($p = 0.007$, HR 3.62).

CONCLUSIONS Cranioplasty procedures should be performed at least 14 days after initial craniectomy to minimize infection risk. Obtaining intraoperative bone cultures at the time of craniectomy in the absence of clinical infection should be discontinued as the culture results were not a useful predictor of postcranioplasty infection and led to the unnecessary use of synthetic prostheses and increased health care costs.

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KEY WORDS cranioplasty; infection; cryopreserved; intraoperative cultures; PEEK; diagnostic and operative techniques; polyetheretherketone

ABBREVIATIONS ABF = autologous bone flap; +ABF = culture-positive ABF; PEEK = polyetheretherketone; TBI = traumatic brain injury.

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CRANIOPLASTY aims to restore a cosmetic skull defect with either a stored autologous bone flap (ABF) or a custom synthetic prosthesis. This relatively common neurosurgical procedure is associated with complication rates of 15%–35%,^{4,6,8–10,12–20,22–29} with the most frequent complication being postoperative infection. The highest reported clinical infection rate after cranioplasty is 26%.²⁹ As native skin flora (for example, *Staphylococcus* and *Propionibacterium*) represent the most common source of postoperative infection,^{3,29} our institution—along with others⁵—has established a protocol of acquiring intraoperative culture swabs of the removed bone flap at the time of initial craniectomy to screen for microbial contamination before cryopreservation and eventual reimplantation. The potential clinical benefit of this methodology is unknown.² We reviewed our experience at a high-volume tertiary care referral center over the past 10 years to present the largest single-center study on cranioplasty infection to date, with the goal of determining predictors of cranioplasty infections and the clinical utility of intraoperative bone flap cultures.

Methods

The hospital's institutional review board approved this study. We conducted an electronic search of our institution's operative reports and retrospectively examined all cranioplasties performed from March 2004 through November 2014. Each case was then individually reviewed to ensure accuracy. Clinical and radiographic data were recorded. Per protocol at our institution, any post-cranioplasty patient with signs of infection was routinely treated by immediate explantation of the ABF followed by the administration of culture-tailored antibiotics for 6–12 weeks as guided by the infectious disease team. Thus, “post-cranioplasty infection,” for the purposes of this study, is defined as an infection resulting in removal of the ABF.

Intraoperative Bone Swab

Throughout the study period, our standard institutional protocol during the initial craniectomy was to obtain a culture swab of the extracted ABF prior to its placement in cytostorage for the future cranioplasty procedure. If the ABF was unsalvageable (for example, a fragmented, open fracture with environmental contamination, invasion by tumor, and so forth), a swab was not obtained and the ABF was not cryopreserved. Cultures were monitored during the patient's recovery to screen for microbial contamination of the ABF. During the study period, we employed 2 consecutive protocols for the use and interpretation of the intraoperative swab culture results: A) From March 2004 through June 2013, any culture-positive ABF (+ABF), regardless of organism, was discarded and a custom synthetic prosthesis was implanted at the time of cranioplasty. B) From July 2013 through November 2014, any ABF with a skin flora organism was not discarded. Instead, cryopreservation was maintained after the +ABF was soaked in bacitracin (50,000 U in 500 ml saline) for 10 minutes prior to freezing. During thawing and prior to reimplantation, the ABF was again soaked in bacitracin for at least 10 minutes and subjected to a 3-minute soak in betadine solution as well.

Statistical Analysis

Statistical analysis was performed using SPSS version 19 (IBM Corp.). Cox proportional-hazards regression models were used to analyze variables potentially influencing the risk of infection. A *p* value < 0.01 was considered significant.

Results

Over the 10.75-year period, 754 cranioplasty procedures were performed. Four-hundred fifty-five patients were male (60%), and the average patient age was 44 years (range 1–86 years). Six hundred forty patients were managed under protocol A and 114 patients under protocol B. Indications for craniectomy are shown in Table 1, with traumatic brain injury (TBI) as the leading indication in 51.4% (388) of cases. The median time from craniectomy to cranioplasty was 123 days (range 2–9855 days). Median follow-up after cranioplasty was 237 days for protocol A (range 7 days–10 years) and 225 days for protocol B (range 30–480 days).

Material Used for Cranioplasty

A sterile ABF was used in 532 cases (70.6%). A synthetic flap was used in 222 cases (29.4%). Eighty-nine +ABFs were discarded during the time of protocol A in favor of a synthetic flap, but 37 +ABFs were reimplanted during the period of protocol B. The material used for the synthetic prostheses subgroup varied (Table 2), with polyetheretherketone (PEEK) as the most common. The indication for a synthetic prosthesis varied: 71 (32%) for an initial unsalvageable ABF, 39 (17.6%) for an ABF removed after intracranial infection (for example, brain abscess, elective craniotomy infection), 4 (1.8%) due to tumor invasion of the ABF, and 19 (8.5%) at the discretion of the treating physician. However, the leading indication for implantation of a synthetic flap was a culture-positive bone swab (+ABF) from the original craniectomy in the absence of clinical suspicion for infection in 89 cases (40.1%) during the study period under protocol A.

Postcranioplasty Infection

The overall infection rate after cranioplasty was 6.6% (50 cases) occurring at a median postoperative Day (POD) 31 (range 8–2035 days). Eleven cases (22%) occurred after POD 90. Causative organisms are listed in Table 3. Isolated Gram-positive infections were the most common (58%), whereas isolated Gram-negative infections were cultured in 18% of cases and polymicrobial infections in 16% of cases. *Staphylococcus* spp. were the causative organisms in 62% of cases.

Cranioplasty material did not affect the postcranioplasty infection rate, as there was no significant difference among sterile ABFs (7%), +ABFs (8%), and synthetic prostheses (5.5%; *p* = 0.425; Table 2). A cranioplasty procedure ≤ 14 days after the initial craniectomy was the only significant predictor of postcranioplasty infection (*p* = 0.007, HR 3.62). The following factors were evaluated but were found to not statistically influence postoperative infection: age; sex; indication for original craniectomy; cranioplasty performed at ≤ 30, ≤ 90, or > 90 days after craniectomy; shunt placement during cranioplasty; postcranioplasty

TABLE 1. Indication for craniectomy in a population of 754 cranioplasty patients

Indication	No. (%)
TBI (depressed skull fracture, extraaxial hematoma, intra-axial hematoma, &/or diffuse swelling)	388 (51)
Ischemic stroke w/ malignant edema	73 (10)
Intraparenchymal hemorrhage (spontaneous or AVM)	104 (14)
Subarachnoid hemorrhage	102 (14)
Spontaneous brain abscess	5 (1)
Tumor	22 (3)
Postop infection of a previous craniotomy	39 (5)
Other	21 (3)

AVM = arteriovenous malformation.

hydrocephalus requiring a separate shunting procedure; postoperative seizures; postoperative hematoma requiring evacuation; and place of discharge after cranioplasty. Neither did the type of synthetic material used influence the postoperative infection rates within the synthetic cranioplasty subgroup ($p = 0.986$; Table 2).

Intraoperative Bone Culture

Culture swabs taken at the time of initial craniectomy were available for 640 subsequent cranioplasties. One hundred fourteen ABFs were not salvageable due to gunshot wound, open depressed skull fracture, infection of prior craniotomy, initial craniectomy at an outside facility, and so forth. One hundred twenty-six ABFs (20%) were culture positive (+ABF). Eighty-nine +ABFs occurred during protocol A and were discarded, and a synthetic prosthesis was used at cranioplasty. Thirty-seven +ABFs occurred under protocol B and were replaced at the time of cranioplasty after a bacitracin and betadine soak.

The 37 +ABFs reimplanted under protocol B had cultures positive for *Propionibacterium acnes* (22 cases), coagulase-negative *Staphylococcus aureus* (9 cases), *Propionibacterium acnes* and coagulase-negative *Staphylococcus aureus* (2 cases), *Micrococcus* (1 case), *Diphtheroids* spp. (1 case), *Candida parapsilosis* (1 case), and *Bacillus* spp. (1 case). There were 3 postcranioplasty infections (8%) after +ABF operations under protocol B, a rate similar to the overall infection rate for all cranioplasty proce-

TABLE 3. Causative organisms in 50 cranioplasty infections

Organism	No.
Isolated single Gram-positive infection (n = 29)	
MRSA	12
MSSA	11
<i>Propionibacterium</i>	4
<i>Staphylococcus epidermidis</i>	1
Group A strep	1
Isolated single Gram-negative infection (n = 9)	
<i>Morganella morganii</i>	1
<i>Serratia marcescens</i>	2
<i>Enterobacter</i>	2
<i>Escherichia coli</i>	3
<i>Pseudomonas</i>	1
Polymicrobial infection (n = 8)	
MSSA, <i>Fusobacterium nucleatus</i>	1
CoNS, <i>Streptococcus milleri</i> , <i>Candida albicans</i>	1
MRSA, MSSA, <i>Propionibacterium</i>	1
MRSA, <i>Proteus mirabilis</i>	1
CoNS, MSSA	1
MSSA, <i>Candida</i>	1
<i>Propionibacterium</i> , <i>Fingoldia magna</i> , <i>Enterobacter aerogenes</i>	1
<i>Propionibacterium</i> , MSSA	1
No culture growth	2
Cranioplasty removal at outside hospital	2

CoNS = coagulase-negative *Staphylococcus aureus*; MRSA = methicillin-resistant *S. aureus*; MSSA = methicillin-sensitive *S. aureus*.

dures (Table 2). All 3 +ABF infections under protocol B were caused by organisms that were different from those in the original intraoperative bone culture from the initial craniectomy.

Discussion

Cranioplasty is a common neurosurgical procedure that, given the implantation of nonliving tissue (whether ABF or synthetic prosthesis), carries a risk of complica-

TABLE 2. Material used for 754 cranioplasties and the rate of infection

Cranioplasty Material*	No. (%)	No. of Observed Infections (%)	Hazard Ratio	95% CI
Sterile ABF	495 (66)	35 (7)	[1.00]†	
+ABF	37 (5)	3 (8)	1.33	(0.41, 4.34)
Synthetic material‡	222 (29)	12 (5)	0.67	(0.34, 1.33)
PEEK	151 (68)	9 (6)	[1.00]†	
Porex	24 (11)	1 (4)	0.77	(0.10, 6.12)
Methylmethacrylate only	7 (3)	0 (0)	0.00	
MedPor	23 (10)	2 (9)	1.48	(0.31, 7.00)
Other	17 (8)	0 (0)	0.00	

MedPor = porous polyethylene; Porex = porous high-density polyethylene.

* $p = 0.425$.

† Reference.

‡ $p = 0.986$.

tions such as surgical site infection. The use of intraoperative bone culture at the time of craniectomy is thought to indicate whether the initial ABF is sterile for future reimplantation. After reviewing our large series of cranioplasty procedures, we found no significant association between +ABF and postcranioplasty infection. The overall infection rate of 6.6% is slightly lower than the 7.9% rate reported in a recent systematic review.²⁸ Notably, 22% of the postcranioplasty infections in the present study occurred more than 90 days after the index procedure and would not be considered surgical site infections under the guidelines of the Centers for Disease Control and Prevention's National Healthcare Safety Network.

Ultra-early cranioplasty (≤ 14 days after initial craniectomy) was the only patient or procedural variable associated with postcranioplasty infection. Importantly, it is one of the few variables over which the treating physician has control. Previous studies have reported conflicting results regarding the impact of the timing of cranioplasty on infection rates.^{4,15,20,22,24,25,29} A large systematic review²⁸ failed to show any statistically significant influence on infection when comparing "early" (< 3 months) and late cranioplasty. However, small sample sizes limited the statistical power of that review, and the time to cranioplasty evaluated was only 3 months. The influence of ultra-early (≤ 14 days) cranioplasty has not been evaluated in the literature.

In our series, ultra-early cranioplasty was performed during the initial hospitalization for craniectomy, after the resolution of cerebral edema. In these cases, there was a logistical desire by both the physician and the patient's family to replace the ABF during the primary hospitalization rather than after discharge. The total number of patients (27) who underwent an ultra-early cranioplasty was relatively small, but the infection rate of 18.5% among this group was significant and probably represents an avoidable risk. Replacing the bone flap 30 days later, which would still be considered early according to several previous studies, did not confer additional infection risk. Such timing is favored by some centers given reports of functional improvement after early cranioplasty.^{1,7,11,21} Our data suggest that the ideal time for early cranioplasty, if desired, is probably between 14 and 30 days to balance the risk of infection with neurocognitive improvement since interrupting the wound healing process earlier than 14 days seems to predispose to subsequent wound complications.

In cases of synthetic prostheses, the choice of material did not impact the risk of infection in our series. A recent international, multiinstitutional report of 66 PEEK prostheses demonstrated an infection rate of 7.6%.²¹ The postcranioplasty infection rate among 151 PEEK implants in our series was 6%, and, as in other studies, suggests that synthetic prostheses have infection rates similar to those with ABFs.^{4,14,19,23,25,27–29}

Most important in our results is the favorable comparison between protocols A and B as regards the reimplantation of +ABFs despite intraoperative bone cultures of skin flora. Specifically, there was no increased risk of postcranioplasty infection in cases in which a +ABF was reimplanted, and there was no concordance between the organisms from the few postcranioplasty infections using

+ABF and the original intraoperative cultured organisms at the time of craniectomy. Another smaller study⁵ also reported no increased risk of infection from the reimplantation of +ABFs and no agreement between the intraoperative cultures at the time of craniectomy and the causative organism of the postcranioplasty infection.

These results have significantly changed our institutional practice. During the 9.25 years in the study period under protocol A, 89 synthetic prostheses (the majority PEEK) were implanted instead of +ABFs. As the average cost of a PEEK synthetic prosthesis ranges from \$7550 to \$8350 depending on its size, had these +ABF been reimplanted instead (as was done under protocol B) our center would have saved between \$671,950 and \$743,150, or up to \$80,340 annually. We have since permanently abandoned the practice of routine bone cultures at the time of craniectomy and now adhere to protocol B for all bone flaps in the absence of clinical infection.

This study has several limitations. First, while it is the largest cranioplasty series to date, it is still a single-center study primarily composed of patients with TBI and vascular malformation. Additionally, its retrospective nature obviates a proper control group, though the comparison between patients under protocol A and those under protocol B served as a comparison between the 2 reimplantation strategies. Lastly, we defined postcranioplasty infection as an infection requiring cranioplasty explantation. It is possible that patients with minor or superficial infections were not included in our analysis, though the practice of treating such infections with antibiotics and not just explanting the flap is not routine at our institution and probably has a negligible impact on our results. Finally, our protocol B reimplantation strategy included soaking the flap in betadine. While the efficacy of this step is untested and the possibility of untoward influences (such as on reabsorption) is unknown, we cannot generalize our results to the reimplantation of +ABF without such treatment.

Conclusions

Intraoperative bone culture at the time of craniectomy is not a clinically useful predictor of postcranioplasty infection, and its elimination may reduce the substantial cost of unnecessary synthetic prostheses. Cranioplasty procedures should be performed at least 14 days after the initial craniectomy to minimize infection risk.

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Disclosures

Dr. Chesnut is a consultant for Orsan, Neuroptics, and Innerspace.

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Conception and design: Morton, Abecassis, Nerva, Emerson, Ene, Chowdhary, Levitt, Ko, Dellit, Chesnut. Acquisition of data: Morton, Abecassis, Hanson, Nerva, Emerson, Ene, Chowdhary, Levitt, Dellit. Analysis and interpretation of data: all authors. Drafting the article: Morton, Abecassis, Hanson, Barber, Nerva, Emerson, Ene, Chowdhary, Levitt, Ko, Chesnut. Critically revising the article: Morton, Abecassis, Barber, Chowdhary, Levitt, Ko, Dellit, Chesnut. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Morton. Statistical analysis: Morton, Barber, Ko. Administrative/technical/material support: Barber. Study supervision: Morton, Chowdhary, Ko, Dellit, Chesnut.

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