Delayed Cranioplasty: Outcomes Using Frozen Autologous Bone Flaps

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Abstract

Reconstruction of skull defects following decompressive craniectomy is associated with a high rate of complications. Implantation of autologous cryopreserved bone has been associated with infection rates of up to 33%, resulting in considerable patient morbidity. Predisposing factors for infection and other complications are poorly understood. Patients undergoing cranioplasty between 1999 and 2009 were identified from a prospectively maintained database. Records and imaging were reviewed retrospectively. Demographics, the initial craniectomy and subsequent cranioplasty surgeries, complications, and outcomes were recorded. A total of 187 patients underwent delayed cranioplasty using autologous bone flaps cryopreserved at −30°C following decompressive craniectomy. Indications for craniectomy were trauma (77.0%), stroke (16.0%), subarachnoid hemorrhage (2.67%), tumor (2.14%), and infection (2.14%). There were 64 complications overall (34.2%), the most common being infection (11.2%) and bone resorption (5.35%). After multivariate analysis, intraoperative cerebrospinal fluid (CSF) leak was significantly associated with infection, whereas longer duration of surgery and unilateral site were associated with resorption. Cranioplasty using frozen autologous bone is associated with a high rate of infective complications. Intraoperative CSF leak is a potentially modifiable risk factor. Meticulous dissection during cranioplasty surgery to minimize the chance of breaching the dural or pseudodural plane may reduce the chance of bone flap.

Keywords
- cranioplasty
- autologous
- autogenous
- cranial reconstruction
- cerebrospinal fluid

Reconstruction of skull defects (cranioplasty) has become an increasingly common procedure with the advent of recent evidence supporting favorable outcomes from decompressive craniectomy for treatment-refractory intracranial hypertension.[1–3] Perceived benefits include (1) protection of intracranial contents, (2) restoration of cosmesis, and (3) improvement in neurologic function ("syndrome of the sunken skin flap"). Although the surgeon can choose to repair the skull defects using either autologous, allogeneic, or alloplastic implant materials, autologous

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bone has benefits such as being readily available, its capacity for growth and integration into recipient bone without rejection. Other materials pose added costs and morbidity attributed to the use of foreign bodies.[4] New autologous grafts may be harvested from other parts of the calvarium or extracranial sites, but this introduces additional donor-site morbidity. In neurosurgical institutions where suitable storage facilities are available, the skull flap explanted from the craniectomy surgery is preserved in a sterile manner (either by cryopreservation or subcutaneous storage within the patient's body) until such a time where the patient's neurological state has recovered or is stabilized adequately for delayed (interval) cranioplasty.

To date, studies comparing outcomes of cranioplasty with cryopreserved and subcutaneously stored flaps have produced variable results; a significant deficiency being the lack of standardization between described techniques.[5] Although this procedure is possibly the least technically demanding in the spectrum of neurosurgical procedures, it is ironically associated with significant complications, often requiring repeat surgical intervention. In particular, high infection rates have been reported; a phenomenon which remains poorly understood.

Traditionally, the preferred method of delayed cranioplasty in our institution involves the use of cryopreserved autologous bone. We have evaluated the clinical outcomes and complications of cranioplasties using cryopreserved autologous bone flaps performed over a 10-year period and analyzed potential risk factors for infection.

Patients and Methods

Patients who underwent cranioplasty procedures within the Western Australia Interhospital Neurosurgical Service were identified by searching a prospectively maintained database between 1999 and 2009. This service administers neurosurgical care for the state's population (2.4 million) through three major public teaching hospitals (Sir Charles Gairdner Hospital, Royal Perth Hospital, and Princess Margaret Hospital). Case records, imaging studies, and relevant laboratory microbiology were reviewed for all the identified patients. Data variables were selected to investigate potential risk factors for complications (►**Table 1**).

A single dose of antibiotic prophylaxis was administered on induction of anesthesia as standard protocol. Patients had their initial postoperative consultation approximately 6 weeks after discharge and reviewed thereafter as required. Due to the centralized nature of the neurosurgical services, patients with complications such as late infection and resorption were readily identified. For the purposes of the current study, an intraoperative cerebrospinal fluid (CSF) leak, defined as leak into the surgical field at the time of surgery, was identified based on operative records and includes both intentional and unintended release of CSF. An "infection" was defined as surgical site infection requiring operative removal of the bone flap, and "resorption" was defined as bone flap resorption requiring revision surgery.

Table 1 Data collated for analysis of infection risk factors

Preoperative
Age, sex, smoking status, GCS, mobility, tracheostomy tube in situ, PEG tube in situ Medical comorbidities: diabetes, hypertension, heart disease, lung disease, immune status Indication for initial craniectomy Interval of time between craniectomy and delayed cranioplasty
Intraoperative
Cranioplasty material (autologous bone, titanium, methylmethacrylate, combination, other) Site, duration of surgery, use of antibiotic prophylaxis, intraoperative CSF leak
Postoperative
Complications (CSF leak, infection, resorption, extra-axial fluid collection requiring evacuation, return to theater, seizures) Follow-up period, cosmetic outcome

Abbreviation: CSF, cerebrospinal fluid; GCS, glasgow coma scale.

Statistical Methods

Data were analyzed using the R environment for statistical computing.[6] Descriptive statistics are shown where appropriate. Univariate and multivariate regressions were conducted. Binary logistic regression was used to determine which variables were significantly associated with outcomes. The outcomes investigated were infection, bone resorption, and the overall complication rate. Variables that were significant at a 5% significance level were retained in the final model. Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for these models.

Results

During the study period, 187 patients (male 75.4% and female 24.6%) underwent delayed primary cranioplasty using cryopreserved autologous bone and were available for evaluation. There were 165 (88.2%) adults and 22 (11.8%) pediatric patients. Indications for craniectomy were trauma (77.0%), stroke (16.0%), subarachnoid hemorrhage (2.67%), tumor (2.14%), and infection (2.14%). Unilateral hemicraniectomy was performed in 117 (62.6%) patients and bifrontal craniectomy in 70 (37.4%) patients.

Following the initial craniectomy, median interval to cranioplasty was 66 days (range 10–390 days). 121 (64.7%) cranioplasties were performed within 90 days of craniectomy, whereas 66 (35.3%) cases occurred beyond 90 days. These were classified as "early" and "late," respectively. Late cases occurred on a case-by-case basis when the patient was not yet deemed neurologically or medically stable until that point. Mean operation duration was 115 minutes. An intraoperative CSF leak into the surgical wound occurred in 64 cases (34.2%).

A total of 64 (34.2%) complications were recorded in the 187 patients (►**Table 2**). Infection resulting in removal of the bone flap was the most common complication (11.2%). Other

Table 2 Complications following cranioplasty

Complication	% and number of patients
Infection requiring removal of bone	11.2 (21)
Resorption requiring revision surgery	5.34 (10)
Extra-axial collections requiring surgical evacuation	5.34 (10)
Superficial wound infections	3.21 (6)
Contour irregularity not related to infection or resorption	3.21 (6)
Postoperative shunting	3.21 (6)
Seizures	2.67 (5)

complications included skull flap resorption requiring revision surgery (5.34%), extra-axial fluid collections requiring evacuation (5.34%), superficial wound infection not requiring removal of the bone (3.21%), postoperative hydrocephalus (3.21%), and seizures (2.67%). In this series of patients, there were eight deaths, of which five cases were attributable to surgical mortality (2.67%).

After investigation (►**Table 3**), multivariate analysis indicated an intraoperative CSF leak increased the odds of a patient having a complication (OR, 2.38; 95% CI [1.25, 4.54]; $p = 0.009$). With regard to infection, the odds remained higher in the presence of an intraoperative CSF leak (OR, 4.50; 95% CI [1.67, 12.07]; $p = 0.003$). In addition to this, those patients who did not have a percutaneous endoscopic gastrostomy (PEG) tube in situ were significantly associated with a higher risk of infection (OR, 9.24; 95% CI [1.15, 73.96]; $p = 0.036$). With regard to bone resorption, surgical duration greater than 2 hours (OR, 4.18; 95% CI [1.09, 16.03]; $p = 0.037$) and unilateral sites (OR, 8.90; 95% CI [1.04, 75.93]; $p = 0.046$) were associated with a higher risk of bone resorption.

Discussion

The use of autologous bone flaps to reconstruct large skull defects following craniectomy seems intuitive. Our study, however, highlights significant morbidity and a significant risk of revision surgery in patients undergoing delayed autologous cranioplasty. In particular, the infection rate of 11.2% far exceeded our overall infection rate for all neurosurgical procedures combined (1.7%) during the study period.

We found that when an intraoperative CSF leak occurred into the surgical field (34.2%), the risk of infection was increased significantly. During the cranioplasty surgery, the subgaleal plane has to be re-established either by diathermy or blunt dissection to facilitate replacement of the skull flap. Inadvertent breach of the dura or the pseudodural fibrotic plane during dissection can result in CSF leakage. This suggests that meticulous surgical dissection is crucial and in cases where the dura or pseudodura is attenuated, leaving a thicker layer of overlying subcutaneous tissue or muscle is preferable to minimize the chance of CSF leakage.

Our study presents a heterogeneous sample population. All cases were deliberately included to present the total caseload of our institution and highlight the breadth of indications for cranioplasty. Furthermore, it was important to assess whether any specific indications had a bearing on the outcomes studied. Various risk factors have previously been proposed to increase the risk of cranioplasty infection. Such identified groups include "nontrauma" patients,[7] tumor patients,[8] the interval to cranioplasty,[9,10] larger defects,[11] and sinus exposure.[12] It has been argued that "nontrauma" and tumor patients are often older and consequently have increased brain atrophy, a larger potential subdural space, and additional medical comorbidities. These factors were not found to be significant in the current study although sinus exposure was not specifically studied. Regarding the interval to cranioplasty, a period of 3 to 6 months has been traditionally recommended for reasons such as avoiding surgery on a potentially contaminated wound during the acute phase and allow healing of the soft tissues adjacent to the craniectomy defect.[9,10,13] There has been a recent movement toward earlier cranioplasty (within 3 months) given the higher infection rates identified with the traditional late approach,[7,14] perhaps due to reduced viability of the bone flap after prolonged storage. Early cranioplasty also minimizes the risk of cerebral blood flow-related ("sunken skin flap") complications. Overall, there is limited evidence available to enable a significant conclusion. Until multivariate analysis in a prospective fashion on a large scale is available, clinical judgment on a case-by-case basis will prevail. In our study, each patient was assessed individually on clinical and radiologic grounds to enable cranioplasty as early as possible; resolution of cerebral edema and no active medical issues contraindicating intervention. Late cases represented a group of patients deemed neurologically or medically unstable up until the point of intervention. In our data, early or late cranioplasty did not appear to have a significant impact on infection risk.

A review of the literature reveals highly variable rates of infections among complications reported for autologous cranioplasty (►**Table 4**). Various methods can be employed for storage of the explanted skull flap. Cryopreservation is the most commonly reported form of sterile bone storage, theoretically preserving structural proteins of bone, haversian systems, and maintaining viability of osteoblast-like cells that contribute and induce host cells to form new bone, rather than just act as a scaffold for host bone to grow over.[15–17] Our literature review reveals no international consensus on the optimal method of cryopreservation; there is great variability in temperature settings, cooling methods, and "dry" or "wet" methods of storage using antibiotics or cryoprotective agents. A recent study surveying major neurosurgical institutions similarly concluded there were significant variations in the techniques and conditions for skull flap storage.[18] Cryoprotective agents can be used to protect cells against theoretical injury from freezing due to intracellular ice formation, recrystallization during warming, and alterations in intra- and extracellular solutions.[19] Recent animal studies have demonstrated increased viability of

Table 3 Multivariate analysis of risk factors

Outcome	Infection requiring removal					Bone resorption					Overall complications				
Variable	Univariate		Multivariate			Univariate		Multivariate			Univariate		Multivariate		
	OR	95% CI	OR	95% CI	*p*-Value	OR	95% CI	OR	95% CI	*p*-Value	OR	95% CI	OR	95% CI	*p*-Value
Age															
40–60 vs. < 40	0.64	0.20–2.04	–	–	NS	0.48[a]	0.10–2.31	–	–	NS	0.53	0.25–1.15	–	–	NS
> 60 vs. < 40	0.42	0.05–3.40	–	–				–	–		0.93	0.32–2.67	–	–	
> 60 vs. 40–60	0.66	0.07–6.33	–	–				–	–		1.74	0.52–5.78	–	–	
CSF leak intraoperative															
Yes vs. no	2.92	1.16–7.37	4.50	1.67–12.07	0.003	3.08	0.84–11.33	–	–	NS	2.17	1.15–4.08	2.38	1.25–4.54	0.009
CSF leak postoperative															
Yes vs. no	4.1	0.36–47.27	–	–	NS	N/A		–	–	NS	N/A		–	–	NS
Interval to cranioplasty															
≤ 90 vs. > 90 d	1.1	0.42–2.88	–	–	NS	1.29	0.32–5.16	–	–	NS	1.27	0.67–2.41	–	–	NS
Duration of surgery															
> 2 vs. ≤ 2 hours	0.81	0.28–2.36	–	–	NS	2.65	0.73–9.55	4.18	1.09–16.03	0.037	1.16	0.59–2.26	–	–	NS
Mobility impaired															
Yes vs. no	0.7	0.27–1.82	–	–	NS	0.61	0.151–2.43	–	–	NS	1.610	0.86–3.01	–	–	NS
Sex															
Male vs. female	0.79	0.29–2.18	–	–	NS	3.07	0.38–24.89	–	–	NS	1.4	0.67–2.89	–	–	NS
Trauma indication															
Trauma vs. nontrauma	1.31	0.42–4.11	–	–	NS	2.8	0.35–22.73	–	–	NS	1.64	0.77–3.53	–	–	NS
Extra-axial fluid collection															
Yes vs. no	2.08	0.41–10.52	–	–	NS	N/A		–	–	NS	NA		–	–	NS
PEG tube in situ															
No vs. yes	6.45	0.84–49.59	9.24	1.15–73.96	0.036	1.15	0.23–5.62	–	–	NS	0.76	0.37–1.55	–	–	NS
Tracheostomy in situ															
Yes vs. no	0.71	0.23–2.22	–	–	NS	0.77	0.16–3.75	–	–	NS	1.59	0.80–3.18	–	–	NS
Smoker															
Yes vs. no	1.66	0.60–4.62	–	–	NS	0.97	0.20–4.78	–	–	NS	0.75	0.35–1.64	–	–	NS
Site															

(*Continued*)

Table 3 (*Continued*)

Outcome	Infection requiring removal					Bone resorption					Overall complications				
Variable	Univariate		Multivariate			Univariate		Multivariate			Univariate		Multivariate		
	OR	95% CI	OR	95% CI	*p*-Value	OR	95% CI	OR	95% CI	*p*-Value	OR	95% CI	OR	95% CI	*p*-Value
Unilateral vs. bifrontal	0.51	0.20–1.26	–	–	NS	5.8	0.72–46.83	8.90	1.04–75.93	0.046	1.08	0.57–2.02	–	–	NS
Diabetes mellitus															
Yes vs. no	1.48	0.31–7.20	–	–	NS	N/A		–	–	NS	0.34	0.07–1.57	–	–	NS

Abbreviations: CSF, cerebrospinal fluid; N/A, not applicable due to small numbers; NS, no statistical significance.
[a]Age groups 40-60 and > 60 were combined for this analysis to compare two groups (< 40 vs. ≥ 40).

osteogenic cells in fresh and wet cryopreserved bone compared with specimens that were deep frozen only.[20] Furthermore, bacteria have been shown to survive freezing,[17] so any contamination during storage cannot be assumed to be eradicated. Our institution's protocol for bone storage is to clean the harvested bone in saline, wrap in plastic sheets, and store in a dry box at − 30°C. Then at the time of reimplantation, the bone is allowed to thaw out at room temperature, then soaked in Betadine (Betadine® Solution (povidone iodine), Purdue Products L.P., Stamford, CT) immediately before reimplantation. The bone is not autoclaved because this has been associated with an unacceptably high rate of resorption owing to destruction of morphogenetic proteins and osteocytes crucial in osteoinduction.[17,21,22]

Other authors[23–29] have reported success with subcutaneously preserved sites such as the scalp and abdomen. A case study has also used subcutaneous preservation to store an infected bone fragment that was later successfully reimplanted,[30] so-called "autopurification" because the preservation site can be monitored for local signs of infection. The limitations of subcutaneous preservation are the creation of an additional surgical site subject to additional complications, an ongoing risk of resorption while stored in situ, and increased operative time. Furthermore, there is evidence in animal studies suggesting frozen bone has greater mechanical integrity (withstands a higher mechanical load) than fresh bone,[31] and retains more lacunar cellularity than subcutaneously preserved bone.[32] A meta-analysis in 2003 favored use of cryopreserved bone over subcutaneous preservation for such reasons.[32] Although the limited data available on subcutaneous preservation indicates a low infection rate, only a single small retrospective review has noted a statistically significant result compared with frozen bone,[26] and specifically only in the subpopulation of traumatic brain injury. In this study, there were 0/19 cases of infection in the subcutaneous preservation group versus 4/14 cases of infection in the cryopreservation group. Of note, there was no significant difference between the two groups in their overall patient population.

To date, there are no prospective studies comparing the two methods. A systematic review of the literature before 2011 conducted in a retrospective, nonrandomized fashion noted no difference in cranioplasty infection rates based on method of autograft storage, type of material, or timing of cranioplasty.[33]

There were several unexpected findings in this study. In our series, 41 patients had PEG tubes in situ at the time of cranioplasty, and only 1 of these 41 cases developed cranioplasty infection. The odds of infection were lower in the PEG tube group after multivariate analysis. We had initially hypothesized that the presence of a PEG tube may act as a source of seeding and thus be associated with increased infection risk, however in retrospect, it is possible that patients who were not fed by PEG tubes may have had under-recognized malnutrition thus predisposing to a higher risk of infection. It was also found that patients who underwent unilateral craniectomy were at higher risk of skull bone resorption. We speculate that this observation may be due to more

Table 4 Literature review of autologous cranioplasties

Author	Cranioplasties	Preservation method	Infection, % (*n*)	Resorption, %	Overall complication rate (%)
Dry cryopreservation					
Grossman et al[34]	12	CP − 80°C, neomycin irrigation	0.00%	0.00%	0.00%
Cheng et al[13]	175	CP no temp specified	4.60% (8)	N/A	15.4%
Iwama et al[22]	49	CP − 35 or − 84°C	2.00% (1)	2.00% (1)	4.10%
Asano et al[15]	46	CP − 40°C	10.9% (5)	15.2% (7)	26.0%
Lee et al[35]	118	CP − 70°C	5.90% (7)	N/A	N/A
Schuss et al[36]	280	CP − 80°C	N/A	N/A	16.4%
Lu et al[37]	16	CP − 80°C	0.00%	N/A	N/A
Inamasu et al[26,a]	31	CP − 70°C	16.1% (5)	N/A	N/A
Sobani et al[38]	65	CP − 27°C	N/A	N/A	N/A
Wet cryopreservation					
Nagayama et al[9]	206	CP − 16°C + amikacin	3.90% (8)	N/A	N/A
Osawa et al[17]	27	CP − 80°C + gentamicin/ amikacin sponge + autoclaved	3.70% (1)	7.40% (2)	11.1%
Prolo and Oklund[21]	53	CP − 20°C or − 70°C with bacitracin-soaked sponge	3.80% (2)	3.80% (2)	9.40%
Shimizu et al[39]	39	CP + DMSO	2.60% (1)	38.4% (15)	N/A
Im et al[40]	83	CP − 71°C + ethylene oxide gas sterilization or hydrogen peroxide and alcohol soaks	7.23% (6)	19.4% (15)	N/A
Matsuno et al[10]	54	CP − 20°C with 100% ethanol + autoclaved	25.9% (14)		
SC					
Häuptli, Segantini[28]	42	SC	2.30% (1)	4.70% (2)	N/A
Inamasu et al[26,a]	39	SC	5.10% (2)	N/A	N/A
Flannery and McConnell[23]	12	SC	5.00% (1)	0.00%	5.00%
Movassaghi et al[25]	53	SC	3.80% (2)	N/A	N/A
Morina et al[29]	75	SC	2.67% (2)	N/A	12.0%
Not specified					
Josan et al[41]	16	N/A	12.5% (2)	N/A	N/A
Manson et al[12]	17	N/A	24.0% (4)	N/A	29.0%
Gooch et al[11]	57	N/A	N/A	6.50% (4)	N/A
Lee et al[42]	91	N/A	5.50% (5)	N/A	6.60%
Tokoro et al[43]	38	N/A	2.60% (1)	N/A	N/A
Paşaoğlu et al[27]	27	N/A	0.00%	0.00%	0.00%
Shoakazemi et al[24]	89	N/A	5.60% (5)	2.20% (2)	24.0%
Archavlis and Carvi Y Nievas[44]	200	N/A	N/A	N/A	15.0%
Moreira-Gonzalez et al[8]	312	N/A	7.10% (22)	N/A	N/A
De Bonis et al[45]	135	N/A	8.90% (12)	7.41% (10)	N/A
Beauchamp et al[46]	57	N/A			

Abbreviations: CP, cryopreservation; *n*, number; N/A: not available; SC, subcutaneous.
[a]Presented both cryopreservation and subcutaneous methods separately.

frequent incorporation of the temporal part of the skull in the standard decompressive craniectomy which is often performed in the trauma setting (as compared with a typical bifrontal decompression). As this is the thinnest part of the skull, bone resorption is more apparent and affects cosmesis, particularly due to the presence of temporalis muscle atrophy that is quite common after a cranioplasty.

Conclusion

Cranioplasties using frozen autologous skull flaps are associated with a disproportionately high rate of complications. There are few predictive clinical factors we can augment to influence this. A review of the literature has highlighted a lack of consensus regarding bone preparation and storage practices for the harvested autologous bone. Further research should be directed toward an improved understanding of skull bone biology and bone cryostorage practices, areas which are currently understudied, to determine their influence on cranioplasty complications.

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