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OBJECTIVE Cranioplasty is a technically simple procedure, although one with potentially high rates of complications. The ideal timing of cranioplasty should minimize the risk of complications, but research investigating cranioplasty timing and risk of complications has generated diverse findings. Previous studies have included mixed populations of patients undergoing cranioplasty following decompression for traumatic, vascular, and other cerebral insults, making results challenging to interpret. The objective of the current study was to examine rates of complications associated with cranioplasty, specifically for patients with traumatic brain injury (TBI) receiving this procedure at the authors’ high-volume level 1 trauma center over a 25-year time period.

METHODS A single-institution retrospective review was conducted of patients undergoing cranioplasty after decompression for trauma. Patients were identified and clinical and demographic variables obtained from 2 neurotrauma databases. Patients were categorized into 3 groups based on timing of cranioplasty: early (≤ 90 days after craniectomy), intermediate (91–180 days after craniectomy), and late (> 180 days after craniectomy). In addition, a subgroup analysis of complications in patients with TBI associated with ultra-early cranioplasty (< 42 days, or 6 weeks, after craniectomy) was performed.

RESULTS Of 435 patients identified, 141 patients underwent early cranioplasty, 187 patients received intermediate cranioplasty, and 107 patients underwent late cranioplasty. A total of 54 patients underwent ultra-early cranioplasty. Among the total cohort, the mean rate of postoperative hydrocephalus was 2.8%, the rate of seizure was 4.6%, the rate of postoperative hematoma was 3.4%, and the rate of infection was 6.0%. The total complication rate for the entire population was 16.8%. There was no significant difference in complications between any of the 3 groups. No significant differences in postoperative complications were found comparing the ultra-early cranioplasty group with all other patients combined.

CONCLUSIONS In this cohort of patients with TBI, early cranioplasty, including ultra-early procedures, was not associated with higher rates of complications. Early cranioplasty may confer benefits such as shorter or fewer hospitalizations, decreased financial burden, and overall improved recovery, and should be considered based on patient-specific factors.

Prior studies investigating the ideal timing of cranioplasty with respect to the occurrence of complications such as infection, hydrocephalus, and postoperative hematoma have reported varied results, and this issue remains an area of continued debate. “Ultra-early” cranioplasty, defined as less than 6 weeks after decompression, would allow many patients to undergo cranioplasty during their initial hospitalization rather than being discharged and having to return for a second procedure. The advantages of
early cranioplasty, if not associated with an increased risk of complications, would therefore include a wider selection of posthospital facilities, removal of the financial burden of returning to the hospital for additional surgery, and possibly an improved neuropsychological recovery.2,12–16

Many studies examining the timing of cranioplasty have included patients who originally underwent decompressive craniectomy for varied causes, including ischemic stroke, intracerebral hemorrhage, aneurysmal subarachnoid hemorrhage, or tumor, in addition to patients suffering traumatic brain injury (TBI).3,8,17–19 This diversity makes it difficult to interpret study results when considering the specific population of patients with TBI. The objective of the current study was to examine complication rates associated with cranioplasty for patients with TBI undergoing this procedure at our institution over a 25-year time period (October 1995 through April 2020) in 3 time ranges: early (≤ 90 days after craniectomy), intermediate (91–180 days after craniectomy), and late (> 180 days after craniectomy). In addition, we conducted a subgroup analysis of complications in TBI patients associated with ultra-early cranioplasty (< 42 days, or 6 weeks, after craniectomy).

Methods
Study Population

After receiving approval from our IRB, we performed a retrospective review of cranioplasties performed at Harborview Medical Center, a level 1 trauma center in Seattle, Washington. All patients who originally underwent cranioplasty for trauma were included in the analysis. We used 2 databases to identify these patients. First, we included patients with TBI receiving cranioplasties from October 1995 through November 2014, a subset of our previously reported review of all cranioplasties performed for any indication at our institution.8 Second, we reviewed a separate neurotrauma database of patients who underwent decompressive craniectomy and subsequent cranioplasty via a Kempe incision from August 2015 through April 2020. From both sources, we obtained patient demographics (age, sex), timing of cranioplasty, and postoperative complications, including new-onset seizures, radiographic or clinical evidence of hydrocephalus that did not exist prior to cranioplasty, hematoma, or infection. To provide a sense of our institutional tendency for when we perform cranioplasties, we grouped patients according to time between initial trauma and cranioplasty using 15-day increments. Then, using the definitions provided in a recent consensus statement for determining the timing of cranioplasty and grouping patients for analysis,20 we categorized patients into 3 groups based on timing of cranioplasty: early (≤ 90 days), intermediate (91–180 days), and late (> 180 days) cranioplasty. We also performed a subanalysis on patients who underwent cranioplasty < 42 days after their initial decompression (ultra-early group).

Determination of Patient Readiness for Cranioplasty

Determining cranioplasty timing at our institution is multifactorial and ultimately determined by surgeon preference. Our institution’s approach is to have discharged patients followed at 4–6 weeks after their initial decompression to determine readiness for cranioplasty. If the patient remains in the hospital at that time, they are generally considered for readiness at that time. It should be noted that if a patient had a specific reason to be considered for early cranioplasty, such as discharge readiness or concern for syndrome of the trephined, that decision would have been made by the surgeon on an individual basis. In general, at our institution, patients must meet certain criteria to be deemed appropriate for cranioplasty. A screening set of laboratory tests, including white blood cell count, erythrocyte sedimentation rate, C-reactive protein, and potentially urinalysis, blood cultures, or other specific tests are sent, as dictated by any clinical concern. Patients with any type of infection are not considered for cranioplasty until treatment of the infection has been completed. Patients must also show appropriate platelet counts and coagulation factors. Antiplateletants and anticoagulants are discontinued prior to cranioplasty; the decision of when to restart these agents is guided by the indication for their use. Finally, there should be no concerns regarding wound breakdown or poor wound healing. Patients are evaluated clinically and also routinely undergo noncontrast head CT to determine readiness. If the parenchyma is below the inner table of the patient’s skull, the patient is immediately considered for cranioplasty. If fullness is apparent and appears related to ventriculomegaly or an extraventricular fluid collection, we will consider intraoperative drainage with a Dandy needle or use a lumbar drain to allow flap replacement. These options are frequently considered for patients in whom ventricular enlargement may represent ex vacuo ventriculomegaly versus hydrocephalus, when skull reconstruction might assist in determining the need for CSF diversion. We routinely store all flaps in our facility’s bone bank. If the patient’s flap is either infected or unusable for structural reasons such as comminuted fracture, a synthetic polyetheretherketone implant is custom-made for the patient when he or she is determined to be ready for cranioplasty.

Statistical Analysis

Student t-test and ANOVA tests were performed to compare means of continuous variables. Fisher’s exact test was performed to evaluate categorical variables. Univariate logistic regression analyses were performed to test for associations between timing of cranioplasty surgery and clinical outcome variables. Timing of cranioplasty surgery was analyzed as a categorical variable, separating patients into 3 separate time points (0–90 days, 91–180 days, and > 180 days). A p value < 0.05 was considered statistically significant. Statistical analysis was performed using R (version 4.0.3, R Foundation for Statistical Computing).

Results

A total of 435 patients were included in the analysis. We grouped patients by 15-day increments to provide a sense of when we tend to perform cranioplasties based on the protocol described above (Fig. 1). We then grouped patients using the consensus guidelines.20 141 patients underwent early cranioplasty, 187 patients underwent intermediate cranioplasty between 91 and 180 days, and
107 patients underwent late cranioplasty (Table 1). In the overall study population, the mean rate of postoperative hydrocephalus was 2.8%, the rate of seizure was 4.6%, the rate of postoperative hematoma was 3.4%, and the rate of infection was 6.0%. The total complication rate for the entire population was 16.8%. There was no significant difference in complication rates among the 3 groups (Table 2).

We performed a univariate logistic regression analysis to identify any differences between the early group and the intermediate and late groups combined. No statistically significant relationship was identified between early cranioplasty and any of the listed complications (Table 3).

A subgroup analysis of 56 patients who underwent ultra-early cranioplasty (< 42 days) was performed. No statistically significant differences in postoperative complications were found comparing the ultra-early group with all other patients combined (Table 4).

Discussion
We present our 25-year experience of cranioplasties in trauma patients, with a focus on the relationship between timing and complication rates. Our results for this cohort of patients with TBI found a complication rate of 16.8% overall, similar to that reported by other studies, which report a range in complication rates from 16% to 35%.3–11 We found no difference in postoperative complications related to timing of cranioplasty for procedures performed at early (≤ 90 days) versus intermediate (91–180 days) or late (> 180 days) time ranges in our cohort of patients with TBI.

Timing of Cranioplasty
Many, but not all, studies have divided patients between those who underwent cranioplasty before or after 3 months postcraniectomy, defining procedures performed before 3 months postcraniectomy as “early,” but the definition of “early” in regard to cranioplasty remains a matter of debate. Given the inconsistent definitions of early cranioplasty, there has been an overall lack of clear direction. For this reason, a consensus statement was recently produced at the International Conference on Recent Advances in Neurotraumatology. The statement confirmed that more study is needed to investigate and identify the ideal timing for cranioplasty for specific clinical conditions,20 and suggested the following definitions for future research: ultra-early, < 6 weeks or 42 days after craniectomy; early, 6 weeks to 3 months after craniectomy; intermediate, 3–6 months after craniectomy; and delayed, > 6 months after craniectomy.20 Our study used these definitions in grouping patients for analysis.

Overall Complication Rates
Prior studies have attempted to determine the optimal timing for cranioplasty to reduce complications and optimize outcomes, but the results are often inconsistent.
Some studies, including two meta-analyses, report no significant difference in overall complication rates between cranioplasties performed early versus late, using approximately 3 months as a cutoff between groups.\(^2\),\(^7\),\(^9\),\(^21\) However, several other reports contradict this finding. Tora et al. reported a higher complication rate for cranioplasties performed within 90 days of craniectomy, including a higher reoperation rate for any cause; in their TBI subgroup, the odds of any complication decreased when cranioplasty was delayed.\(^1\) Chaturvedi et al.\(^4\) and Schuss et al.\(^10\) also found higher complication rates with earlier cranioplasty, defining early as < 3 months and < 2 months, respectively. The inconsistent nature of these results may be multifactorial. The larger studies included cranioplasties performed for any reason, rather than specifically for the trauma population. Of the studies and subanalyses specifically focusing on patients with TBI, the sample sizes were small, including fewer than 150 patients. Additionally, the definition of early was inconsistent. Our report describes the largest cohort of trauma-specific patients to date and uses consensus-based definitions to promote consistency.

**Specific Complications Associated With Cranioplasty Timing**

While it would likely be advantageous to most patients to undergo cranioplasty at their initial hospitalization, patients must not be put at increased risk of complications as a result of earlier cranioplasty. Complications of interest include infection, postoperative hydrocephalus, hematomas, and new-onset seizures.

One of the most studied complications of cranioplasty is postoperative surgical site infection, which generally requires removal of the implant. Historically, cranioplasty was often performed at least 6 months after decompression with concerns over infection commonly cited as the benefit of delay.\(^2\),\(^14\),\(^22\) Cheng et al. reported a statistically significant association between earlier cranioplasty and infection in their autologous cranioplasty group, but the difference in timing was not well defined, and the patient group was a small mixed population.\(^23\) Morton et al. reported a significantly higher infection rate with cranioplasty within 14 days of the original craniectomy,\(^4\) which was also in a mixed population, and is a shorter time frame than even our ultra-early group. Other reports did not find increased infection rates associated with earlier cranioplasties. Similar to our results, no difference in infection rate was seen between early and late cranioplasty groups in two mixed-population meta-analyses;\(^2\),\(^21\) or in several studies using an approximate 3-month cutoff between early and late groups.\(^3\),\(^9\),\(^11\),\(^24\),\(^25\) Oh et al. also studied a mixed population, which had a higher infection rate in their late group (cranioplasty > 90 days after craniectomy), but this did not remain significant after multivariate regression.\(^19\) The most effective way to mitigate infection is careful attention to individual patient risk factors, such as existing extracranial infections or concerns about breakdown of the craniectomy wound. Any concerns should prompt a delay of the cranioplasty.

Development of hydrocephalus requiring placement of permanent CSF diversion (such as a ventriculoperitoneal shunt) has been raised as a concern, with some research suggesting that early timing of cranioplasty may increase the risk of hydrocephalus.\(^3\),\(^8\),\(^11\) In our previous report of a mixed-presentation cohort, we found that the hydrocephalus rate was increased with earlier cranioplasty, and was most common in patients who underwent cranioplasty

### TABLE 2. Complications of the study population by timing of cranioplasty

<table>
<thead>
<tr>
<th>Complication</th>
<th>Total Population, n = 435</th>
<th>Early, n = 141</th>
<th>Intermediate, n = 187</th>
<th>Late, n = 107</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postop hydrocephalus</td>
<td>12 (2.8%)</td>
<td>5 (3.5)</td>
<td>5 (2.7)</td>
<td>2 (1.9)</td>
<td>0.81</td>
</tr>
<tr>
<td>Seizure</td>
<td>20 (4.6%)</td>
<td>5 (3.5)</td>
<td>7 (3.7)</td>
<td>8 (7.5)</td>
<td>0.30</td>
</tr>
<tr>
<td>Hematoma</td>
<td>15 (3.4%)</td>
<td>5 (3.5)</td>
<td>6 (3.2)</td>
<td>4 (3.7)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Infection</td>
<td>26 (6.0%)</td>
<td>11 (7.8)</td>
<td>7 (3.7)</td>
<td>8 (7.5)</td>
<td>0.21</td>
</tr>
<tr>
<td>Any complication</td>
<td>73 (16.8%)</td>
<td>25 (17.7)</td>
<td>22 (11.8)</td>
<td>20 (18.7)</td>
<td>0.18</td>
</tr>
</tbody>
</table>

### TABLE 3. Univariate logistic regression model evaluating the impact of early cranioplasty, as compared to all intermediate- and late-timed cranioplasties, on multiple clinical outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>OR (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postop hydrocephalus</td>
<td>1.51 (0.44–4.81)</td>
<td>0.49</td>
</tr>
<tr>
<td>Seizure</td>
<td>0.68 (0.22–1.81)</td>
<td>0.471</td>
</tr>
<tr>
<td>Hematoma</td>
<td>1.04 (0.32–3.0)</td>
<td>0.938</td>
</tr>
<tr>
<td>Infection</td>
<td>1.57 (0.68–3.49)</td>
<td>0.274</td>
</tr>
<tr>
<td>Any complication</td>
<td>1.29 (0.74–2.21)</td>
<td>0.352</td>
</tr>
</tbody>
</table>

### TABLE 4. Demographics and morbidity of the study population by ultra-early cranioplasty versus all other periods

<table>
<thead>
<tr>
<th>Variable</th>
<th>Ultra-Early, n = 56</th>
<th>Early, Intermediate, or Late, n = 379</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age ± SD, yrs</td>
<td>54.2 ± 21.3</td>
<td>50.8 ± 15.4</td>
<td>0.15</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>40 (71.4)</td>
<td>287 (75.7)</td>
<td>0.51</td>
</tr>
<tr>
<td>Postop hydrocephalus</td>
<td>2 (3.6)</td>
<td>10 (2.6)</td>
<td>0.66</td>
</tr>
<tr>
<td>Seizure</td>
<td>3 (5.4)</td>
<td>17 (4.5)</td>
<td>0.73</td>
</tr>
<tr>
<td>Hematoma</td>
<td>3 (5.4)</td>
<td>12 (3.2)</td>
<td>0.42</td>
</tr>
<tr>
<td>Infection</td>
<td>3 (5.4)</td>
<td>23 (6.1)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Any complication</td>
<td>11 (19.6)</td>
<td>56 (14.8)</td>
<td>0.33</td>
</tr>
</tbody>
</table>

\(^*\) Ultra-early: < 6 weeks; early, intermediate, or late: ≥ 6 weeks.
within 90 days of craniectomy. Similar results were reported by Tora et al. Malcolm et al. also found an increased rate of hydrocephalus in patients with cranioplasty within 90 days of craniectomy, both in the overall patient population within their mixed-population meta-analysis, and also within the trauma subgroup analysis. Other studies report contrary findings. One meta-analysis, focusing specifically on postcranioplasty hydrocephalus, found that for patients undergoing decompressive craniectomy for TBI, there was a lower rate of hydrocephalus in patients who underwent cranioplasty in <90 days compared to >90 days. This same relationship was not found for patients undergoing craniectomy for other etiologies. The inconsistency in these reports may be related to some confusion in the etiology of hydrocephalus in the TBI population. As an example, the earlier correlation between early cranioplasty and hydrocephalus that we reported in a mixed population was likely to have been related to a tendency to perform cranioplasty early in patients with ventriculomegaly, to assist in guiding the differential diagnosis of ventricular enlargement and the requirement for shunting. In that study, patients were noted to have hydrocephalus as a complication of cranioplasty regardless of preoperative presence of hydrocephalus. In contrast to our earlier report, our present study of an expanded TBI-specific cohort showed no differences between craniotomy timing and development of hydrocephalus.

For this analysis, we differentiated between posttraumatic hydrocephalus, which existed prior to cranioplasty, and postcranioplasty hydrocephalus, which occurred de novo after replacing the flap. The latter was rare in our population, occurring in only 2.8% of all patients. Patients with hydrocephalus prior to cranioplasty were not included in our hydrocephalus rate as a complication. In those cases, the hydrocephalus is believed to be a sequel of the trauma and initial decompression rather than of the cranioplasty itself. Because of an institutional preference, we almost never place shunts prior to cranioplasty, as we prefer to analyze the cranioplasty’s effect on the ventriculomegaly before committing the patient to a shunt.

Another area of interest is the possible association of new seizures with cranioplasty timing. No difference in seizure rates between early and late groups was reported in the meta-analysis by Malcolm et al. This finding is consistent with our results, which show no difference in risk of new seizures associated with timing of craniotomy. In the prior report from our institution’s diverse population, postoperative seizures occurred only in those patients with cranioplasty >90 days postcraniectomy; however, seizure risk appeared to be more closely associated with the reason for the craniectomy rather than the timing of the procedure.

Prior mixed-population studies have suggested that there is no significant difference in postoperative hematoma rates between early and late cranioplasty. Our study supports these findings.

Benefits of Early Cranioplasty

Some prior studies have argued that cranioplasties performed before 3 months are safe, and our results are in agreement with these findings. The potential benefits from early cranioplasty are many and diverse. Many postacute care facilities are reticent to accept patients with skull defects, limiting options for these patients. Patients often balk at wearing protective headgear. After hospital discharge, returning patients to the hospital for a cranioplasty is expensive and may be problematic, particularly if the patient is located in a resource-limited setting. Flaps stored subcutaneously undergo time-related resorption, interfering with or preventing delayed autologous cranioplasty.

Finally, early cranioplasty becomes desirable if it facilitates neuropsychological recovery. Several reports have demonstrated that patients have improved clinical conditions following cranioplasty. Early cranioplasty has been shown to provide cognitive benefits and may optimize a patient’s rehabilitation course. Studies have shown improvement in performance on activities of daily living as well as in their Glasgow Outcome Scale and Mini-Mental State Examination after cranioplasty. Such reports suggest that the syndrome of the trephined is a continuum wherein some patients may have mild manifestations that do not prompt the diagnosis, but that do respond to calvarial reconstruction. Given this, it is likely that many of our patients with TBI would likely benefit from early cranioplasty, if it can be performed safely. While our study does not provide evidence that early cranioplasty is necessarily superior to later cranioplasty, it does show that it is not associated with a higher rate of complications. We would therefore argue that if an individual patient would benefit from an earlier procedure, the risk of complications should not be a reason to delay.

Ultra-early cranioplasty, performed less than 42 days after the initial decompression, could allow an even larger number of patients with TBI to undergo cranioplasty during the initial hospitalization. Our study performed a subgroup analysis for patients receiving cranioplasties <42 days after decompression and identified no differences in complications for this subgroup compared with all other patients in our cohort.

Limitations and Future Direction

This study has several limitations related to the retrospective design. Patients were not randomized and the timing of cranioplasty was influenced by perception of clinical readiness by the surgical team. Generalizability of the results is limited as the design is a single-center study, including only patients who underwent craniectomy for trauma. However, our intent in focusing on this population was to obtain data relevant to this subgroup in order to address conflicting study results published to date, which may be due, in part, to diverse study populations. A prospective comparative-effectiveness multicenter study to further elucidate the implications of cranioplasty timing on complication rates would be beneficial. Additionally, while our data allowed for an initial analysis of ultra-early cranioplasty, we were limited by the small number of patients and were not able to appropriately power the study to allow rigorous comparisons and conclusions. Ultra-early cranioplasty may be safe, but warrants further investigation. We also recognize that factors other than timing may influence outcomes; for example, we included pa-
patients from our database of those who underwent Kempe incisions. A separate analysis on the effects of operative techniques on outcomes may be of interest.

Conclusions

Earlier cranioplasty following decompressive craniectomy for TBI is not associated with a higher rate of complications compared with intermediate or later procedures. The decision of when to perform cranioplasty is best determined by patient-specific factors rather than duration of time after craniectomy. In the appropriately chosen patient, early cranioplasty may confer benefits such as decreased hospital length of stay and improved neurological recovery.

Acknowledgments

We would like to thank Sharon Durfy, PhD, for her assistance with manuscript preparation.

References


Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Chesnut, Eaton, Bonow. Acquisition of data: Eaton, Caldwell, Robinson. Analysis and interpretation of data: Eaton, Nistal, Temkin. Drafting the article: Eaton, Greil, Aljuboori. Critically revising the article: Chesnut, Eaton, Greil, Bonow. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Chesnut. Statistical analysis: Nistal, Temkin. Study supervision: Chesnut, Bonow.

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