Is There An Optimal Time for Performing Cranioplasties? Results from a Prospective Multinational Study

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BACKGROUND: The optimal timing of cranioplasty remains uncertain.

OBJECTIVE: We hypothesized that the risk of infections after primary cranioplasty in adult patients who underwent craniectomies for non—infection-related indications are no different when performed early or delayed. We tested this hypothesis in a prospective, multicenter, cohort study.

METHODS: Data were collected prospectively from 5 neurosurgical centers in the United Kingdom, Malaysia, Singapore, and Bangladesh. Only patients older than 16 years from the time of the non—infection-related craniectomy were included. The recruitment period was over 17 months, and postoperative follow-up was at least 6 months. Patient baseline characteristics, rate of infections, and incidence of hydrocephalus were collected.

RESULTS: Seventy patients were included in this study. There were 25 patients in the early cranioplasty cohort (cranioplasty performed before 12 weeks) and 45 patients in the late cranioplasty cohort (cranioplasty performed after 12 weeks). The follow-up period ranged between 16 and 34 months (mean, 23 months). Baseline characteristics were largely similar but differed only in prophylactic antibiotics received (P = 0.28), and primary surgeon performing cranioplasty (P = 0.15). There were no infections in the early cranioplasty cohort, whereas 3 infections were recorded in the late cohort. This did not reach statistical significance (P = 0.55).

CONCLUSIONS: Early cranioplasty in non-infection—related craniectomy is relatively safe. There does not appear to be an added advantage to delaying cranioplasties more than 12 weeks after the initial craniectomy in terms of infection reduction. There was no significant difference in infection rates or risk of hydrocephalus between the early and late cohorts.

INTRODUCTION

The optimal timing of cranioplasty has been an area of debate within the neurosurgical faculty. Anecdotal and limited evidence from proponents of late cranioplasty suggests that such a strategy favors a lower risk of infection. Others disagree and believe that an early cranioplasty is just as safe and justifiable. The reality is that the optimal timing of cranioplasty remains uncertain. There are conflicting data regarding the complication rates with either early or late cranioplasty. Moreover, all studies published are retrospective and reflect either a single institution’s experience or a case series of a single surgeon.

Our study aimed to prospectively study the rate of infections in cranioplasty performed before and after 12 weeks. To our knowledge, this is the first prospective, multicenter observational study comparing the infection rates between early and late cranioplasty.

Key words
- Cranioplasty
- Early versus late
- Infection
- Timing

Abbreviations and Acronyms
PEEK: Polyether ether ketone

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METHODS

Data were collected prospectively from 5 participating neurosurgical centers, which included Queen’s Hospital (Romford, United Kingdom), St Mary’s Hospital (London, United Kingdom), National University Hospital (Singapore), United Hospital Limited (Dhaka, Bangladesh), and Hospital Pulau Pinang (Penang, Malaysia). There was no randomization process and the patients were not divided equally among the participating centers. Patients were recruited on admission for the cranioplasty procedure and were divided into 2 cohorts depending on the length of time between craniectomy and cranioplasty. The early cranioplasty cohort had the cranioplasty performed within 12 weeks of the craniectomy, whereas the late cranioplasty cohort had the procedure after 12 weeks. The primary outcome studied was the rate of infection after primary cranioplasty in adult patients. The U.S. Centers for Disease Control and Prevention criteria and definition for surgical site infection were adopted. We included only adult patients aged 16 years and older at the time of the craniectomy. Any form of cranioplasty material was allowed and the choice was not influenced in any way by this study. Implant material selection was left to the preference of the individual recruitment center. Patients were excluded if they had undergone a previous cranioplasty at the same site or if the indication for craniectomy was an infective process. The recruitment period was 17 months, from January 2013 to June 2014. Patients were followed up in the postoperative period for a minimum of 6 months after the cranioplasty.

A key point to this study was the fact that we chose not to disclose the definition of early and late cranioplasty to the participating centers to avoid any influence on the timing of the procedure. Also, the indications, timing, and type of implants used in the cranioplasty procedures were at the discretion of the consultant neurosurgeons in charge and were not influenced by this study. Patient baseline characteristics were also collected, which included age, gender, antibiotic prophylaxis regime, primary surgeon, type of implant, the indication for craniectomy, and duration of surgery. Data were collected and tabulated in a proforma. Data were analyzed using IBM SPSS Statistics version 21 (IBM Corp., Armonk, New York, USA). The P values were calculated with the \( t \) test except when the expected value was less than 5, in which case the Fisher exact test was used. Univariate analysis was used to test for covariates predictive of cranioplasty infection. Only factors that were found to be predictive in univariate analysis (\( P < 0.2 \)) were entered into a multivariate logistic regression analysis. Significance was established at the 95% level. All data handling was in accordance with the United Kingdom Data Protection Act 1998.

RESULTS

A total of 73 patients were recruited into the study: 31 patients recruited from the United Kingdom between January 2013 and February 2014, 30 patients recruited from Malaysia between May 2013 and June 2014, 9 patients from Singapore between July 2013 and December 2013, and 3 patients recruited from Bangladesh in April 2014. Three patients from the Malaysian cohort did not meet the inclusion criteria because they were younger than 16 years at the time of craniectomy and were therefore excluded. This gave a total of 70 patients, with 25 patients in the early cranioplasty cohort (range, 3–12 weeks; mean, 8 weeks), and 45 in the late cranioplasty cohort (range, 13–108 weeks; mean, 71 weeks). One patient who made excellent recovery after an aneurysmal subarachnoid hemorrhage at 22 years of age returned to the clinic only after 20 years for a cranioplasty. This patient was initially adverse to the procedure, resulting in delayed cranioplasty. Patient ages ranged between 16 and 74 years (mean age, 40 years; standard deviation, 15.8). There were 20 women and 50 men. Despite the initially planned requirement for a follow-up period of at least 6 months, we managed to follow up patients postoperatively from the time of cranioplasty to 1 November 2015 (range, 16–33 months; mean, 23 months). Four types of implant material were used in this study: autologous bone, titanium, acrylic, and polyether etherketone (PEEK). Our study did not influence the choice of implants. Thirty-one patients underwent cranioplasty using autologous bone, titanium was used in 28 patients, acrylic in 6, and PEEK in 5. Two different regimens of antibiotic prophylaxis existed in all centers with 51 patients (12 patients in the early cranioplasty cohort and 39 patients in the late cohort) receiving single-dose prophylactic antibiotics at induction of anesthesia and 19 patients (13 patients in the early cranioplasty cohort and 6 patients in the late cohort) receiving a regime of 3 doses of antibiotics; the first dose of prophylactic antibiotics was administered at induction of anesthesia and a further 2 doses after 8-hour intervals. Antibiotics used were either first-generation or second-generation cephalosporin. The consultant was the primary surgeon in 28 cases and the registrar in 42 cases. Sixty-eight percent of the early cranioplasty procedures were performed by the consultant compared with 24% of cases in the late cranioplasty cohort. The indication for craniectomy for each patient was collected and divided into 4 broad categories, which included trauma, intracerebral hemorrhage, malignant middle cerebral artery (ischemic) infarct, and “others.” Forty-seven patients (68%) underwent craniectomy because of trauma, 9 patients (13%) because of intracerebral hemorrhage, 8 patients (10%) because of infarcts, 2 patients because of aneurysmal subarachnoid hemorrhage, 2 patients because of cerebral edema after removal of tumors (meningioma and craniopharyngioma), 1 patient because of an atraumatic subdural hematoma, and 1 patient because of hemorrhage from an arteriovenous malformation. The last 6 patients (9%) constituted the group of patients labeled as “Others.” The 2 patients with aneurysmal subarachnoid hemorrhage had craniotomies performed for aneurysm clipping that were converted to craniectomies because of concurrent intracerebral hematomas and brain swelling. Because of the various procedure lengths, the analyzed durations of cranioplasty surgery were divided into 3 groups. Two patients were in the first group with a surgical duration of less than 1 hour, 43 patients in the second group with surgical duration between 1 and 2 hours, and 25 patients in the third group with surgery lasting more than 2 hours.

There was no statistically significant difference in age, sex, implant type, duration of surgery, or indication for craniectomy between the early and late cohorts (Table 1). However, there was a significantly higher proportion of patients who received 3 doses of prophylactic antibiotics (early, 52%; late, 13%; \( P < 0.001 \)) and significantly more patients with
consultant-led surgeries (early, 68%; late, 24%; \( P < 0.001 \)) in the early cranioplasty cohort.

Three infections occurred in the late cranioplasty cohort (4.3%), whereas no infections were recorded in the early cranioplasty cohort. This did not reach statistical significance (\( P = 0.55 \)). All the 3 patients with infections had different implant types (1 autologous, 1 titanium, and 1 PEEK cranioplasty), and the indication for craniectomy was trauma in 2 and malignant middle cerebral artery territory infarct in 1. All these patients had their implants removed followed by treatment with a prolonged course of antibiotics, and none had a repeat cranioplasty procedure during the course of this study. One patient in the late cranioplasty cohort suffered from postcranioplasty hydrocephalus, unrelated to infection, which required a ventriculoperitoneal shunt. None of the recruited patients had preexisting hydrocephalus or a preexisting shunt. There were no deaths in either group, and no patient was taken back to the operating theatre for removal of hematomas.

Univariate analysis of the covariates (ie, implant type, duration of surgery, surgeon category, indication of craniectomy, or antibiotic prophylaxis regime) failed to show a \( P \) value of < 0.2 for any variable (see Table 1). Moreover, no infections were recorded in the early cranioplasty cohort. Analysis using logistic regression models was therefore inappropriate and not performed.

### Table 1. Baseline Patient Characteristics and Relationship Between Presence of Infection and Variables

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>Early Cranioplasty Cohort, n (%)</th>
<th>Late Cranioplasty Cohort, n (%)</th>
<th>( P ) Value</th>
<th>Infection, n (%)</th>
<th>No Infection, n (%)</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients (%)</td>
<td>25 (36)</td>
<td>45 (64)</td>
<td>0.44</td>
<td>3 (6)</td>
<td>66 (94)</td>
<td>0.99</td>
</tr>
<tr>
<td>Mean age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(&lt;35) years</td>
<td>14 (20)</td>
<td>29 (41)</td>
<td></td>
<td>2 (3)</td>
<td>41 (59)</td>
<td></td>
</tr>
<tr>
<td>(35)–(55) years</td>
<td>10 (14)</td>
<td>12 (17)</td>
<td></td>
<td>0 (0)</td>
<td>21 (30)</td>
<td></td>
</tr>
<tr>
<td>(&gt;55) years</td>
<td>1 (2)</td>
<td>4 (6)</td>
<td></td>
<td>1 (1)</td>
<td>5 (7)</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td>0.50</td>
<td></td>
<td></td>
<td>0.34</td>
</tr>
<tr>
<td>Male</td>
<td>18 (26)</td>
<td>31 (44)</td>
<td></td>
<td>3 (4)</td>
<td>46 (66)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>7 (10)</td>
<td>14 (20)</td>
<td></td>
<td>0 (0)</td>
<td>21 (30)</td>
<td></td>
</tr>
<tr>
<td>Implant type</td>
<td></td>
<td></td>
<td>0.53</td>
<td></td>
<td></td>
<td>0.33</td>
</tr>
<tr>
<td>Autologous</td>
<td>11 (16)</td>
<td>20 (29)</td>
<td></td>
<td>1 (1)</td>
<td>30 (43)</td>
<td></td>
</tr>
<tr>
<td>Titanium</td>
<td>10 (14)</td>
<td>18 (26)</td>
<td></td>
<td>1 (1)</td>
<td>27 (39)</td>
<td></td>
</tr>
<tr>
<td>Acrylic</td>
<td>1 (2)</td>
<td>5 (6)</td>
<td></td>
<td>0 (0)</td>
<td>6 (9)</td>
<td></td>
</tr>
<tr>
<td>Polyether ether ketone</td>
<td>3 (4)</td>
<td>2 (3)</td>
<td></td>
<td>1 (1)</td>
<td>4 (6)</td>
<td></td>
</tr>
<tr>
<td>Antibiotic prophylaxis</td>
<td>(&lt;0.001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single dose</td>
<td>12 (17)</td>
<td>39 (56)</td>
<td></td>
<td>3 (4)</td>
<td>48 (69)</td>
<td>0.38</td>
</tr>
<tr>
<td>3 doses</td>
<td>13 (19)</td>
<td>6 (9)</td>
<td></td>
<td>0 (0)</td>
<td>19 (27)</td>
<td></td>
</tr>
<tr>
<td>Primary surgeon</td>
<td>(&lt;0.001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.21</td>
</tr>
<tr>
<td>Consultant</td>
<td>17 (24)</td>
<td>11 (16)</td>
<td></td>
<td>0 (0)</td>
<td>28 (40)</td>
<td></td>
</tr>
<tr>
<td>Registrar</td>
<td>8 (11)</td>
<td>34 (49)</td>
<td></td>
<td>3 (4)</td>
<td>39 (56)</td>
<td></td>
</tr>
<tr>
<td>Duration of surgery</td>
<td>0.83</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.95</td>
</tr>
<tr>
<td>(&lt;1) hour</td>
<td>1 (2)</td>
<td>1 (2)</td>
<td></td>
<td>0 (0)</td>
<td>2 (3)</td>
<td></td>
</tr>
<tr>
<td>1–2 hours</td>
<td>16 (23)</td>
<td>27 (38)</td>
<td></td>
<td>2 (3)</td>
<td>41 (59)</td>
<td></td>
</tr>
<tr>
<td>(&gt;2) hours</td>
<td>8 (11)</td>
<td>17 (24)</td>
<td></td>
<td>1 (1)</td>
<td>24 (34)</td>
<td></td>
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<tr>
<td>Indication for craniectomy</td>
<td>0.99</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.58</td>
</tr>
<tr>
<td>Trauma</td>
<td>17 (24)</td>
<td>30 (44)</td>
<td></td>
<td>2 (3)</td>
<td>45 (64)</td>
<td></td>
</tr>
<tr>
<td>Intracerebral hematoma</td>
<td>3 (4)</td>
<td>6 (9)</td>
<td></td>
<td>0 (0)</td>
<td>9 (13)</td>
<td></td>
</tr>
<tr>
<td>Infarct</td>
<td>3 (4)</td>
<td>5 (6)</td>
<td></td>
<td>1 (1)</td>
<td>7 (10)</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>2 (3)</td>
<td>4 (6)</td>
<td></td>
<td>0 (0)</td>
<td>6 (9)</td>
<td></td>
</tr>
</tbody>
</table>

*Others include 2 patients with aneurysmal subarachnoid hemorrhage, 2 patients with cerebral edema after removal of a tumor (meningioma and craniopharyngioma), 1 patient with an atraumatic subdural hematoma, and 1 patient with hemorrhage from an arteriovenous malformation.
DISCUSSION

This study attempted to recreate a more realistic and current clinical practice by collecting data prospectively from 5 different institutions. Our study population was limited to patients older than 16 years because some of the institutions did not have a pediatric service. By excluding pediatric patients, we also avoided other unique confounding issues such as skull growth, a wider implant variety, and perhaps even differing tissue healing potential. We believe that cranioplasty in the pediatric group should be studied separately.

This study showed that there was no significant difference in the infection risk for patients undergoing early or late cranioplasty procedures after non-infection-related craniectomies. There have been only 7 retrospective, single-institution studies, and 2 systematic reviews analyzing the overall complication rates in early and late cranioplasty. Unsurprisingly, some of these studies have provided similar evidence. However, all these previous studies have limitations that have resulted in difficulty drawing any clear conclusions. Rather than studying a specific primary outcome, all previous studies reviewed overall complications. Furthermore, data were collected over a large time frame, ranging from 9 to 13 years in 5 studies. This translated to a low operative rate and patient recruitment rate per year, ranging between 8 and 23 patients per year in 6 studies. Surprisingly, one study did not provide a definition of infection. The follow-up periods in published series were limited (ranging between 3 and 18 months) considering the retrospective study periods mentioned earlier, and 2 studies failed to state the follow-up duration.

Our data provide reasonable evidence to support performing early cranioplasty, after the recovery from the acute insult that led to the craniectomy. This is further reinforced by a reasonably good length of follow-up for each patient (range, 16–33 months; mean, 23 months) over a 34-month study period. In reality, patients would be followed up at the respective institutions for durations that are dictated by their underlying neurosurgical condition. The option for an early cranioplasty during the same admission is also reasonable, whenever conditions are favorable. Early cranioplasty could be performed while awaiting admission to a regional rehabilitation unit and could possibly even facilitate the recovery process in several ways. First, cranioplasty has been proposed to have a positive influence on cerebrospinal fluid hydrodynamics. Waziri et al. suggested that the risk for hydrocephalus is increased by delaying cranioplasty in patients who had undergone decompensative craniectomy for stroke. Piedra et al. could not show any statistical difference in the rate of hydrocephalus between early and late cranioplasty in 2 separate studies. Our data concur with these studies and we have also found that the risk of hydrocephalus was low and not significantly increased in either cohort. Cranioplasty has also been shown to have a positive effect on cerebral blood flow and could be the key in treating cases with syndrome of the trephined and syndrome of the sinking skull flap. In addition, the procedure helps to minimize or alleviate altogether any concerns regarding protection of the underlying brain while nursing and during rehabilitation, because it has been shown to hinder the rehabilitation process. Another retrospective study reported better functional outcomes (Glasgow Outcome Scale) in patients who underwent cranioplasty before 12 weeks.

In our study, both early and late cranioplasty cohorts were largely similar in all but 2 areas. The use of 3 doses of prophylactic antibiotics before cranioplasty was more frequent, as were the occasions of consultant-led surgeries in the early cranioplasty cohort. However, these 2 factors were not found to have statistically significant influence on the rate of infections, as were other covariates such as implant type, indication for craniectomy, and duration of surgery. There were more males in each cohort, which is explained by the higher number of trauma cases requiring craniectomy, with males making up most of the 2 genders in this group (76%; n = 36). The fact that there were no infections in the early cranioplasty cohort is perhaps clinically relevant.

In our experience, the tissue planes are usually better delineated while performing an early cranioplasty and should result in quicker dissection and reduced operating durations. However, we did not find any significant difference in the mean operative time between the early and late cranioplasty cohorts. This finding was in contrast to the results of a recent systematic review in which a meta-analysis of 4 studies showed a significantly reduced operating time in early cranioplasty.

To our knowledge, our study is the first to examine the relationship between the seniority of the surgeon and prophylactic antibiotic regimes against the overall infection rate in early and late cranioplasty. It is also the first to specifically analyze the duration of surgery and its relationship to the rate of infections in early and late cranioplasty.

There are several important limitations to our study. First, it has all the inherent bias of a nonrandomized controlled trial. The number of patients recruited was relatively small and it could be argued that our study was underpowered. This could have led to a type 2 error, leading to the difference between the rate of infections between early and late cranioplasty not reaching statistical significance. However, our patient recruitment rate is the highest per year, compared with all the other retrospective studies to date. The overall infection rate of 4.2% in our study appears to be low, but comparable with the reported rates in several previously published studies, which published ranges between 1.4% and 10.8%. The possible explanations for our low infection rate include underreporting of complications rates by the recruiting centers, patients treated elsewhere for complications arising after the cranioplasty, and a small sample size. However, the likelihood of this is low given our follow-up period. In addition, all infected cases occurred in the late group. There is no agreed definition or scientifically substantiated evidence behind the definition for an early and late cranioplasty. Other studies have used various definitions for early cranioplasty and ranged between 8 and 12 weeks. The surgeons’ reasons behind the timing of cranioplasty were not analyzed. Nevertheless, the definitions of early and late cranioplasty in our study followed the definition used in a previously published systematic review.

We recommend a well-designed prospective randomized controlled study to confirm the findings of our study. Other areas that could be studied are the influence of surgeon experience, prophylactic antibiotics, duration of surgery, and the role of cranioplasty performed during the same admission as the
craniectomy. It would also be interesting to study the psychological and psychosocial impact associated with the cosmetic defect left by a craniectomy.

CONCLUSIONS

Early cranioplasty in non-infection–related craniectomy was not found to be associated with a statistically significant increased risk of infection. Our study could not support a lower risk of infection by delaying cranioplasty for more than 12 weeks after the initial craniectomy. There was no significant difference in infection rates or risk of hydrocephalus between the early and late cranioplasty cohorts. There is a possible relationship between the lower infection rates seen in consultant-led surgery and in patients receiving 3 doses of perioperative antibiotic prophylaxis, although this did not reach statistical significance. We therefore recommend a well-designed prospective randomized controlled study to further evaluate the effect of timing on the complication rates of cranioplasty in both the pediatric and the adult population.

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