Risk factors of aseptic bone resorption: a study after autologous bone flap reinsertion due to decompressive craniotomy

Clinical article

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Object. In patients who have undergone decompressive craniectomy, autologous bone flap reinsertion becomes necessary whenever the cerebral situation has consolidated. However, aseptic necrosis of the bone flap remains a concern. The aim of this study was to report possible perioperative complications in patients undergoing autologous bone flap reinsertion and to identify the risk factors that may predispose the bone flap to necrosis.

Methods. All patients admitted to the authors’ neurosurgical department between September 1994 and June 2011 who received their own cryoconserved bone flap after decompressive craniectomy were studied. The grade of the bone flap necrosis was classified into 2 types. Type II bone necrosis was characterized by aseptic resorption with circumscribed or complete lysis of tabula interna and externa requiring surgical revision. To define predisposing factors, a multivariate analysis was performed using bone necrosis as the dependent variable.

Results. Among the 372 patients (mean age 48.6 years, 57.4% males) who received 414 bone flaps during the observation period, 134 (36.0%) had a diffuse traumatic brain injury, 69 (18.5%) had subarachnoid hemorrhage, 58 (15.6%) had cerebral infarction, 56 (15.1%) had extraaxial bleeding, 43 (11.6%) had intracerebral bleeding, and 12 (3.2%) had a neoplasm. Surgical relevant Type II bone flap necrosis occurred in 85 patients (22.8%) and 91 bone flaps, after a median time of 15 months (interquartile range [IQR], 10–33 months). In a multivariate analysis with Type II necrosis as the dependent variable, bone flap fragmentation with 2 (OR 3.35, 95% CI 1.59–7.01, p < 0.002) or more fragments (OR 24.00, 95% CI 10.13–56.84, p < 0.001), shunt-dependent hydrocephalus (OR 1.76, 95% CI 0.99–3.12, p = 0.04), and a younger age (OR 0.98, 95% CI 0.96–0.99, p = 0.004) was associated with a higher risk for the development of an aseptic bone flap necrosis.

Conclusions. In patients undergoing bone flap reinsertion after craniotomy, aseptic bone necrosis is an underestimated problem during long-term follow-up. Especially in younger patients with an expected good neurological recovery and a fragmented bone flap, an initial allograft should be considered because of an increased risk for aseptic bone flap necrosis.

(http://thejns.org/doi/abs/10.3171/2013.1.JNS12860)

Key Words • craniotomy • cranioplasty • bone flap • aseptic bone flap necrosis • bone resorption

Decompressive craniotomy can be considered a therapeutic option in life-threatening space-occupying intracranial pathologies, such as intracerebral bleeding, and traumatic or ischemic brain swelling when aggressive medical management is not sufficient to alleviate the increasing ICP.¹⁴,¹⁵,¹⁷ In the surviving patients, after resolution of the cerebral swelling and consolidation of the clinical state, cranioplasty with reinsertion of the removed bone flap is performed for mechanical, cosmetic, and therapeutic reasons.¹⁵,¹⁹,¹¹,¹²,¹¹,¹³ While the technique, its complications, and the possible benefit of decompressive cranial surgery have been studied extensively, there are still a lot of open questions concerning the subsequent skull remodeling. Apart from the correct storing of the bone flap, the optimal timing of reinsertion is still under debate. Furthermore, the incidence and the role of possible long-term complications, which require recurrent surgical interventions, need to be elucidated. In particular, progressive aseptic necrosis of the bone flap remains a matter of concern during follow-up, occurring in up to 50% of the patients after cranioplasty.¹,²,³,⁷,¹³ In this context, it would be reasonable to define a “high-risk” patient group that might benefit from an initial allograft. Therefore, it was the aim of this study to report...
possible perioperative complications in patients undergoing bone flap reinsertion after craniotomy and to identify the risk factors predisposing to bone flap necrosis in these patients.

**Methods**

**Patients**

We included 372 patients undergoing bone flap reinsertion after craniotomy (414 bone flaps) admitted to our institution between September 1994 and June 2011. The study was approved by the local ethics committee. Informed consent was not required because of the anonymous, observational, and retrospective nature of the analysis.

**Operation and Follow-Up**

After craniectomy, the removed bone flap was cleaned of adjacent soft tissue, wrapped in sterile cloths, and stored at −80°C. Eighty-five bone flaps were fragmented by a fracture or a former, smaller craniotomy. In these cases, the flap was reconstructed using tiny osteosynthetic titanium plates before freezing it. All bone flaps were routinely cultured during the operation after surgical removal. We reinserted exclusively the flaps that showed no evidence of bacterial contamination. Infected flaps were discarded and not included in the study. All flaps were stored for a median of 78 days.

For reinsertion, the bone flap was passively defrosted in 37°C sodium chloride solution. After reopening the former skin incision, the bony rims of the skull defect and a dural layer were prepared. The bone flap was reinserted and fixed with rigid titanium plates (Biomet). If necessary, CSF was drained from the frontal horn perioperatively. The dural layer was fixed to the bone flap with 3–5 central sutures in all cases to prevent postoperative epidural hematoma. At least 2 nonsuction drains were placed below and above the bone flap so that an outflow of epidural and subgaleal fluid was ensured. These drains were removed within the first 2 postoperative days. All patients received an antibiotic prophylaxis as long as these drains were in place.

Follow-up was scheduled in our outpatient department, according to an institutional protocol, with clinical and CT examinations at 6 weeks, 3 months, 6 months, 12 months, and yearly thereafter. In cases of a suspected or manifest complication, this regimen was varied depending on the clinical and radiological findings. The end point of the data acquisition was the CT diagnosis of a Type II bone flap necrosis (see below). If there were no radiological signs of bony destruction or Type I bone flap necrosis was obvious, the last available CT scan defined the follow-up result.

**Data Acquisition**

Patients’ files and radiological images were screened retrospectively. We created a data set containing information on sex, age at the first operation, diagnosis, period between removal and replacement of the bone flap, size of the bone flap, duration of follow-up, and the presence of a CSF shunt. The diagnosis leading to craniotomy was classified as diffuse brain injury including traumatic brain swelling and traumatic intracerebral hematoma, brain swelling caused by SAH including vasospastic infarction, ischemic stroke (malignant middle cerebral artery infarction), tumor, other spontaneous intracerebral bleeding, and extraaxial hematomas like subacute or chronic subdural hematomas.

The relative 2D size of the trephination defect was calculated by the senior author (C.E.) on a preoperative sagittal radiograph or a sagittal CT scan using the following formula: \( A = \pi/4 \times B \times b \), where \( \pi \) is a constant and \( B \) and \( b \) are the longest diameters of an elliptic area (Fig. 1). To quantify the extent of a possible aseptic bone necrosis, we defined 2 different types of necrosis according to the CT features with W/L 2500/500 HU. A thinning of the bone flap and/or a beginning resorption along the rims of the flap was classified as Type I necrosis, whereas a Type II bone flap necrosis was characterized by a circumscribed, complete lysis of the bone within the flap, including tabula interna and externa with loss of the bony protection of the brain (Fig. 2). According to our institutional protocol, Type II bone flap necrosis was considered to be an indication for surgical revision, with resection of the necrotic bone and implantation of an allograft. The median follow-up duration was 11 months (IQR 2–25 months), with 265 flaps being observed for more than 6 months.

**Statistical Analysis**

Data were analyzed using SPSS version 17.0 software for Windows (SPSS Inc.). Discrete variables are expressed as total number and percentage and continuous variables as mean ± SD or median and IQR unless stated otherwise. Categorical data were compared using the chi-square test or by Fisher exact test, as appropriate. Continuous variables conforming to a normal distribution were compared using Student t-test. Otherwise the Mann-Whitney U-test was applied. Because of its clinical impact, we focused on the surgical relevant Type II bone flap necrosis. To identify possible risk factors, a multivariate logistic regression analysis was performed using Type II bone flap necrosis as the dependent variable. A univariate analysis was performed prior to modeling, and variables were considered if the p value was <0.2. Colinearity between variables was excluded before modeling (R² > 0.7). The variables chosen for the multivariate analysis included age (per year), admission primary diagnosis, period to reinsertion of the bone flap (in months), number of fragments (categorized as 2 or >2 fragments), bilateral versus unilateral bone flap reinsertion, shunt-dependent hydrocephalus, and the size of the bone flap. A Hosmer-Lemeshow test was used to assess the goodness of fit of the multivariate model. Covariates were retained in the model if the p value was <0.2, and the OR and 95% CI were computed. All statistics were 2-tailed, and a p value < 0.05 was considered to be statistically significant.

**Results**

**Patient Characteristics**

Among 372 patients (mean age 48.6 ± 18.4 years;
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57.4% males) who underwent autologous bone flap reinsertion in our institution during the observation period, 134 (36.0%) had a diffuse traumatic brain injury, 69 (18.5%) had SAH, 58 (15.6%) had cerebral infarction, 56 (15.1%) had extraaxial bleeding, 43 (11.6%) had intracerebral bleeding, and 12 (3.2%) had a neoplasm. One hundred forty-one patients (37.9%), in whom 169 flaps were placed, had a shunt-dependent hydrocephalus, with 84 having a CSF shunt implanted before the bone flap reinsertion. In all others the drain was placed within 3 months. In 42 patients (11.3%), bilateral bone flap implantations were necessary. The characteristics of this study group are presented in Table 1.

A total of 414 bone flaps were reinserted after a median of 78 days (IQR 54–113 days), and the mean bone flap size was 85.7 ± 23.06 cm². In 85 cases, fragmented bone flaps were removed during the initial operation due to the severity of trauma and resulting multiple skull fractures. In 43 patients (10.4%) the bone flap consisted of 2 fragments, and in 42 patients (10.1%) there were 3 or more fragments. At the time of reimplantation, the individual parts were rejoined together and placed again as a single bone flap.

Early Complications and Reoperations

Concerning the perioperative complication rate (within the period of hospital stay), 5 patients died after the operation, the causes being pulmonary embolism (n = 3), myocardial infarction (n = 1), and brainstem ischemia (n = 1). The 30-day mortality rate was 1.2%. Furthermore, there were 67 complications during the hospital stay leading to a second surgical intervention. In 24 cases (6.5%), operative revision was necessary for epidural, subdural, or intracerebral bleeding (n = 23). One patient had to undergo reoperation for a subgaleal hematoma. Subdu-
rperitoneal shunting was necessary in 16 cases (4.3%), wound debridement for wound necrosis or deep infection in 26 cases (7.0%), and a re-removal of the bone flap for progressive brain swelling in 1 case (0.3%) (Table 2). A dislocation of the flap during follow-up, requiring a repeat fixation, occurred in 3 patients. Thus, the overall short-term complication rate, referring to operative revisions (n = 67) and the refixation of loosened flaps (n = 3), was 18.8%.

Aseptic Bone Necrosis

On the last CT scans that were available, 131 (31.6%) of 414 bone flaps exhibited the radiological features of Type I bone flap necrosis after a median duration of 19 months (IQR 11–46 months). An aseptic necrosis with complete lysis of the tabula interna and externa (Type II necrosis) occurred in 85 patients (mean age 41.7 ± 19.3, 56.5% males) and 91 bone flaps (21.9%) after a median duration of 15 months (IQR 10–33 months), from the time of bone flap reinsertion onward (Table 3). In all cases, we observed a clinical indication to remove the necrotic bone flap. In patients diagnosed with necrotic flaps, cosmetic disfiguring was the main complaint—for example, for hypermobility of the flap, displacement of osteosynthetic material, or aesthetic reasons. Thirty-nine necrotic bone flaps were resected and replaced by an allograft (titanium in 30, Bioverit in 7, and Palacos in 2 cases). In the remaining 52 cases, the reasons for nonreplacement of the Type II necrotic bone flap were as follows: patient or his/her representative refused the operation (n = 24), patient in a vegetative neurological state (n = 20), and patient lost to follow-up after the initial CT scan (n = 8). Patients in whom necrosis of the reinserted bone flap developed were significantly younger (41.7 ± 19.3 vs 50.6 ± 17.7 years, p = 0.009) (Table 2). Necrotic bone flaps (n = 91) were more likely to be fragmented than those that were not necrotic (Table 2). As a quality control, regular follow-up CT scanning of all nonnecrotic flaps was performed.

Risk Factors for Bone Flap Necrosis

In a multivariate logistic regression analysis with bone flap necrosis Type II as the dependent variable (414 procedures were considered), increasing age was associated with low risk (OR 0.98 [per year], 95% CI 0.96–0.99, p = 0.004) of bone flap necrosis, whereas shunt-dependent hydrocephalus (OR 1.76, 95% CI 0.99–3.12, p = 0.04) and fragmentation into 2 fragments (OR 3.35, 95% CI 1.59–7.01, p < 0.002) or more than 2 fragments (OR 24.00, 95% CI 10.13–56.84, p < 0.001) were associated with a significantly higher risk for a Type II bone flap necrosis (Table 3).

Discussion

Skull remodeling after decompressive craniotomy makes a second operation necessary. For aesthetic, psychological, and economic reasons the autologous bone flap should be the preferred graft. In addition to cosmetic aspects, clinical and neurological improvements have also been described. However, a second operation always carries the risk of new complications, especially in patients who are often weakened by the impact of the initial event, such as brain injury or ischemic stroke. Furthermore, aseptic necrosis of the reinserted bone flap has been reported in 7.2%–50% of the cases, although the reasons for its development are still unknown. Thus, a better understanding of risk factors for the development of bone necrosis after autologous cranioplasty is important.

To our knowledge, this study is the most extensive survey of a large patient group concerning the complications after autologous cranioplasty, paying special attention to necrosis of the bone flap after reinsertion. Because of its retrospective single-institution design, however, there are some limitations that need to be considered. At first, there were multiple physicians involved in the handling of aseptic bone necrosis and in deciding on the replacement of the necrotic bone flap. Until now there has been no standardization of the operative technique and postoperative treatment, but due to a rigid internal protocol a certain scheme for the outpatient follow-up has been fixed. Nevertheless, because 50 patients were lost to follow-up after 1 month, the incidence of long-term complications may be higher than what we have reported.

The methods of measuring the size of the bone flap and quantifying the extent of bone necrosis were not validated, but the fact that a single investigator (senior author) has collected these data can minimize potential errors. It also seems problematic to measure the size of a 3D flap with a formula describing a 2D area. However, it was our aim to investigate the influence of the autograft size on the incidence of aseptic necrosis rather than to define the exact bone flap size. For that reason, it appears to be sufficient to have the relative size of a flap compared with smaller or larger ones.

In this cohort, almost one-quarter (18.8%) of the patients had a procedure-related early postoperative complication, leading to further surgical interventions. However, this rate is within the reported range, depending on the operative technique and the definition of surgery-
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Related complications. Compared with other neurosurgical “standard” procedures, this is a notably high value, and in the authors’ opinion the seriousness of the bone flap reinsertion as a second surgical intervention is still underestimated. Regardless of prolonged aseptic bone necrosis, rebleeding and space-occupying epidural and subdural fluid collections were the most important acute postoperative complications. Especially in patients with a preexisting shunt, a possible negative pressure may facilitate blood collection in a transiently created new space below the bone flap, leading to an acute space-occupying hematoma or chronic epidural or subdural hygroma. For this reason, we always place an epidural drain, as also recommended by other authors. Wound healing problems occurred in 10 patients. Deep infections, especially epidural empyema, occurred in only 4.3% of the cases. Compared with other studies reporting a rate of deep infections between 7% and 12%, our infection rate is low, confirming our prophylactic antibiotic regimen.3,6,21

The main focus of our study, however, was to analyze the incidence of and possible risk factors for aseptic necrosis. Aseptic necrosis is a long-term complication leading to progressive destruction of the bone, with successive cosmetic disfiguring and loss of bony brain protection. As we have mentioned, our data have to be interpreted carefully because there is no overall accepted definition of “bone necrosis” after cranioplasty. In our cohort 222 flaps (53.6%) showed CT signs of an impaired osseous integration: Type I necrosis in 131 and Type II necrosis in 91. Bone necrosis requiring surgical intervention was retrospectively detectable in 21.9% of the implanted bone flaps. The median time to diagnosis in our group was 15 months. Interestingly the median follow-up duration in patients who developed Type I necrosis was 19 months, showing that a beginning resorption of the flap is not necessarily the beginning of a progressive destruction of the bone. However, only 39 flaps were removed and replaced by an allograft. In all other cases, the patients were in a poor neurological condition, were lost to follow-up, or refused a third intervention. In the literature the incidence of delayed aseptic bone necrosis approaches 50%, especially in younger patients with a longer follow-up period.7,10 Thus, time dependency has to be considered, and in the context of this background a follow-up of 2 years seems reasonable.

The resorption rate may appear at first seem higher than expected, but the incidence could be explained by the performance of repeated CT scanning over a short period of time. According to an institutional protocol, clinical and CT follow-up visits were scheduled at 6 weeks, 3 months, 6 months, and 12 months in our outpatient department. The majority of patients were profoundly weakened by

<table>
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<th>Characteristic</th>
<th>No. of Patients</th>
<th>p Value</th>
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<tr>
<td>no. of patients</td>
<td>287</td>
<td>85</td>
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<tr>
<td>mean age in yrs ± SD</td>
<td>50.6 ± 17.7</td>
<td>41.7 ± 19.3</td>
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<tr>
<td>male/female ratio (%)</td>
<td>166 (57.7) to 121 (42.2)</td>
<td>48 (56.5) to 37 (43.5)</td>
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<td>diagnosis (%)</td>
<td>92 (32.4) to 41 (48.2)</td>
<td>55 (19.2) to 14 (16.5)</td>
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<td>diffuse brain injury</td>
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<td>SAH</td>
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<td>10 (11.8)</td>
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<td>36 (12.5)</td>
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<td>extraaxial bleeding</td>
<td>8 (2.8)</td>
<td>4 (4.7)</td>
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<td>intracerebral bleeding</td>
<td>101 (35.2)</td>
<td>40 (47.1)</td>
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<tr>
<td>tumor</td>
<td>251 (87.4) to 36 (12.6)</td>
<td>79 (92.9) to 6 (7.10)</td>
</tr>
<tr>
<td>unilat/bilat ratio bone flap (%)</td>
<td>323</td>
<td>91</td>
</tr>
<tr>
<td>median days to replacement (IQR)</td>
<td>80 (58–115)</td>
<td>74 (46–102)</td>
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<tr>
<td>mean size (cm²) ± SD</td>
<td>85.1 ± 23.06</td>
<td>87.6 ± 23.06</td>
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<td>≤70 (%)</td>
<td>67 (20.7)</td>
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<td>71–90 (%)</td>
<td>140 (43.3)</td>
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<td>81 (25.1)</td>
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<td>&gt;110 (%)</td>
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<tr>
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</tr>
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<td>28 (8.7)</td>
<td>15 (16.5)</td>
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<tr>
<td>&gt;2 fragments</td>
<td>10 (3.1)</td>
<td>32 (35.2)</td>
</tr>
<tr>
<td>median mos to follow-up CT (IQR)</td>
<td>9 (1–23)</td>
<td>15 (10–33)</td>
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the initial trauma, making clinical status an insignificant diagnostic factor. Therefore, we performed regular CT follow-up. An added advantage was being able to monitor the ventricular size and possible increase in ICP. All interventions based on radiographic findings correlated with a clinical complaint at the time of operation. All surgically treated patients exhibited pre-CT clinical symptoms in the presence of an aseptic necrosis.

There are many possible reasons being discussed for progressive necrosis of the reinserted bone flap. We found age, fragmentation, and shunt dependency to be significant and independent predictive parameters for the development of an aseptic bone necrosis. Hence, young patients with a fragmented flap and a CSF shunt in place have the highest risk. Fragmentation is the most critical factor triggering a nutritional deficit of the flap. This also explains the predisposition of patients after severe head injury. Fragmentation and a younger age are associated with a higher risk of bone flap necrosis because many of these patients initially had a serious accident or injury, like a car or bike accident, and in such patients we saw most of the fragmented flaps.

An exact congruity between the bone edge and the bone flap is supposed to be the most important factor for osseous integration of the reinserted necrotic bone. As recommended by Chang et al., the fixation should be as rigid as possible, so we always use mini-osteosynthetic titanium plates for bone flap refixation, as described above.

The impact of exact shunt-dependent hydrocephalus is remarkable, but a definitive cause could not be isolated. We found a study that describes a higher complication rate in such operations after laying an external ventricular drain. Nonphysiological changes of the ICP, possible increase in ICP, all interventions based on radiographic findings correlated with a clinical complaint at the time of operation. All surgically treated patients exhibited pre-CT clinical symptoms in the presence of an aseptic necrosis.

Conclusions

While craniectomy has become an inherent part in the treatment of life-threatening increased ICP, many unanswered questions concerning the following cranioplasty remain. In this retrospective study of a large patient group, we were able to show that complications are not uncommon and that even long-term problems like an aseptic bone necrosis should be considered during follow-up outpatient reassessment. Surgeons and neurologists should not only be aware of the risks of the first operation but also of the cranioplasty. These data have to be reflected in the therapeutic regimen and also in future studies dealing with the effect of decompressive surgery.

This survey shows that bone flap fragmentation, younger age, and shunt dependency are possible risk factors for the development of bone flap necrosis. Further study including long-term data is mandatory, especially concerning the question of whether there is a high-risk patient group that would benefit from an initial allograft.

Disclosure

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 to the study and manuscript preparation include the following. Conception and design: Dünisch. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Dünisch. Statistical analysis: Sakr. Administrative/technical/material support: Kaflff. Study supervision: Ewald.

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Manuscript submitted May 1, 2012. Accepted January 17, 2013. Portions of this work were given in oral presentation form at the 14th European Congress of Neurosurgery, Rome, Italy, October 9–14, 2011. Please include this information when citing this paper: published online March 1, 2013; DOI: 10.3171/2013.1.JNS12860. Address correspondence to: Pedro Dünisch, M.D., Department of Neurosurgery, Hospital of the Friedrich Schiller University, Erlanger Allee 101, 07747 Jena, Germany. email: pedro.duenisch@med.uni-jena.de.