Clinical relevance of current materials for cranial implants

Towards an optimal patient-specific implant material

van de Vijfeijken, S.E.C.M.

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CHAPTER 3

Factors predicting the failure of autologous cranial reconstructions

S.E.C.M. van de Vijfeijken, C. Groot, D.T. Ubbink, W.P. Vandertop, P.R.A.M. Depauw, E. Nout, A.G. Becking; on behalf of the CranioSafe Group

This chapter is based on the publication:
Factors related to failure of autologous cranial reconstructions after decompressive craniectomy

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ABSTRACT

Background: Cranioplasty is customary after decompressive craniectomy. Many different materials have been developed and used for this procedure. The ideal material does not yet exist, while complication rates in cranioplasties remain high. This study aimed to determine factors related to autologous bone flap failure.

Methods: In this two-center retrospective cohort study, 254 patients underwent autologous bone cranioplasty after initial decompressive craniectomy between 2004 and 2014. Medical records were reviewed regarding patient characteristics and factors potentially related to bone flap failure. Data were analyzed using univariable and multivariable regression analysis.

Results: Independent factors related to overall bone flap failure were: duration of hospitalization after decompressive craniectomy [OR: 1.012 (95%CI: 1.003–1.022); p=0.012], time interval between decompressive craniectomy and cranioplasty [OR: 1.018 (95%CI: 1.004–1.032); p=0.013], follow-up duration [OR: 1.034 (95%CI: 1.020–1.047); p<0.001]. In patients with bone flap infection, neoplasm as initial diagnosis occurred significantly more often (29.2% vs. 7.8%; RD 6.5-42.5%) and duration of hospitalization after decompressive craniectomy tended to be longer (means 54 vs. 28 days, MD 26.2 days, 95%CI -8.6 to 60.9 days). Patients with bone flap resorption were significantly younger (35 vs. 43 years, MD 7.7 years, 95%CI 0.8-14.6 years) and their cranial defect size tended to be wider than in patients without bone flap resorption (mean circumference 39 vs. 37 cm; MD 2.4 cm, 95% CI -0.43 to 5.2 cm) and follow-up duration was significantly longer (44 vs. 14 months, MD 29 months, 95%CI 17-42 months).

Conclusion: A neoplasm as initial diagnosis, longer hospitalization after decompressive craniectomy, larger time interval between decompressive craniectomy and cranioplasty and longer follow-up duration are associated with a higher risk of failure of autologous bone flaps for cranioplasty. Patients with these risk factors may be better served with an early recovery program after decompressive surgery or an alloplastic material for cranioplasty.
INTRODUCTION

Decompressive craniectomy is a lifesaving neurosurgical procedure, in which a part of the skull is removed to reduce raised intracranial pressure, resulting from cerebral edema or hemorrhage due to traumatic brain injury, cerebral infarction, subarachnoid hemorrhage, hemorrhagic strokes, neoplasm, or intracranial infections. Following decompressive craniectomy, reconstruction of the cranial defect is mandatory in order to protect the brain, enhance social acceptance, and restore cranial esthetics. Moreover, it may reduce neurologic symptoms, including the syndrome of the trephined and sinking skin flap syndrome.

Autologous bone can be used for cranial reconstructions as it is biocompatible, inexpensive, does not trigger immuno-rejection, and can be effective as a substrate for bony ingrowth and revascularization. In delayed cranial reconstructions, the autologous bone flap is usually stored in a bone bank and re-inserted when the patient is neurologically stable. Storage techniques may significantly alter bone viability; storage temperatures between 8°C and -84°C have been reported. There is no consensus on the optimal time interval between decompressive craniectomy and cranioplasty; different wide-ranging thresholds have been used in the literature.

Reimplantation of preserved autologous bone has a high risk of infection (0%-26%) and bone flap resorption (1%-50%) often resulting in loss of the autologous bone flap.

The aim of this study was to determine independent predictive factors for the failure of autologous bone flaps used for cranioplasty in patients who had undergone decompressive craniectomy.
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MATERIALS AND METHODS

Study design and patient population
In this retrospective case series, 276 consecutive patients were included after a decompressive craniectomy and cranioplasty with autologous bone in separate procedures, performed between January 2004 and December 2014 in two centers [Academic Medical Center (Amsterdam) (n=183) and Elisabeth-Tweesteden Hospital (Tilburg) (n=93)] in the Netherlands. Both centers used identical protocols and procedures that did not change during the study period. Twenty-two patients were excluded because of bilateral defects to conserve homogeneity of the patient group in this study (N=10), or due to lack of follow-up, transfer to a different hospital, which may or may not have been in the Netherlands (N=7), missing data (N=4) and one non-disease related death 21 days after cranioplasty. Thus, a total of 254 consecutive patients were analyzed in this study.

Ethical consideration
This observational study was conducted using the STrengthening the Reporting of OBservational studies in Epidemiology guidelines (STROBE guideline). The study protocol was approved by the medical ethics review board of the AMC (protocol nr. W18_030 # 18.046).

Surgical procedure
After decompressive craniectomy, the removed autologous bone flap was rinsed with 0.9% NaCl, dried with sterile gauze, packed into three sterile transplantation bags, and stored in the local bone bank at -80ºC. Cranioplasty was performed as soon as the patient was medically and neurologically stable, and the wound had fully healed and was free of clinical signs of infection. Thirty minutes before incision, prophylactic antibiotics of a first-generation sodium cephalosporin (Kefzol®, Eurocept) were administered. If possible, the scar of the decompressive craniectomy was reopened and the edges of the cranial defect were made visible and accessible. The autologous bone flap was, if necessary, remodeled by minor adjustments and fixed to the skull, with either sutures or plates and screws. If the temporal muscle was dissected, it was suspended to the inserted autologous bone flap with sutures. A subgaleal drain was inserted for some patients, at the surgeon’s discretion. The skin was closed in two layers and a bandage was applied. All patients underwent standard postoperative care: patients received standard paracetamol post-operative and, if necessary, stronger analgesics were administered. Antibiotics were prescribed postoperatively at the discretion of the surgeon. All patients were seen at least once after the cranioplasty.
Data collection
Clinical data were collected by reviewing the medical records of each patient by two independent researchers (C.G. and S.V.). Extracted parameters were: location of hospital, gender, age at the time of cranioplasty, co-morbidities (diabetes mellitus, cardiovascular disease, or both), smoking habits, initial indication for decompressive craniectomy (cerebrovascular, trauma, neoplasm, infection), time interval between decompressive craniectomy and cranioplasty, length of cranioplasty procedure (scored from scalp incision to closure), duration of hospitalization after decompressive craniectomy and cranioplasty, failure of cranioplasty, in which year the decompressive craniectomy and cranioplasty were performed, and follow-up duration (calculated from the moment of replacement of the autologous bone flap until the last patient contact before December 2014). The neurologic status before and after cranioplasty was not specifically recorded in this study, as it was deemed to have no substantial effect on the outcome of the cranioplasty.

Recorded reasons for autologous bone flap failure included: 1) infection (defined as a clinical infection that required surgical removal), 2) resorption (defined as symptomatic or radiographic resorption where the remaining autologous bone did not protect the brain anymore or the cosmetic outcome was not acceptable), 3) subcutaneous fluid collections, and 4) hemorrhage. A procedure was classified as successful if the autologous bone flap was inserted successfully and no postoperative removal of the autologous bone flap was performed by the end of the study period, or as unsuccessful, in case of the removal of the autologous bone flap.

Defect size measuring
The CT-scans after decompressive craniectomy were retrieved and reviewed. Postoperative 3D virtual models of the CT-scans were rendered in an in-house developed software tool. This tool was developed with C++ in Microsoft Visual Studio 2015 (Microsoft Corporation, Redmond, WA, USA). After reconstructing the 3D-models, landmarks were manually placed on the border of the defect to measure the circumference of the defect (Figure 1).
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Figure 1: Example of cranial defect circumference measurement; in this case 42.6 cm

Statistical analysis
Multivariate stepwise binary logistical regression analyses were used to identify independent predictive factors for failure of autologous bone flaps. Possible predictive factors were derived from the literature. Non-significant factors were manually and sequentially removed until only significant parameters remained. Odds ratios (OR) and their 95% confidence intervals (95% CI) were determined for significant predictive parameters. Univariable analyses were conducted to detect any differences in patients with and without infection or resorption of the bone flap. Differences in continuous variables were expressed as mean differences (MD) with their 95% CIs, differences in dichotomous variables were presented as risk differences (RD) with their 95%CIs. A Number Needed to Treat (NNT) or Number Needed to Harm (NNH) was calculated in case of a significant RD. Statistical analysis was performed with IBM SPSS Statistics 24.0 (Armonk, NY, USA).
RESULTS

Patient characteristics
This study included 254 patients (165 from the Amsterdam University Medical Centers, 89 from the Elisabeth-Tweesteden Hospital) who underwent a decompressive craniectomy and cranioplasty with autologous bone in the period 2004-2014. The median age of the patients was 45 years (IQR: 30–53 years), and 51% were males (n=130). Initial indications for decompressive craniectomy were cerebrovascular (n=125), traumatic brain injury (n=93), neoplasm (n=25), or infection (n=11). Of the included patients 12.2% had a smoking habit at the moment of the cranioplasty, 37.7% did not, 3.1% had quit smoking and in 46.9% smoking habits could not be retrieved. Median follow-up duration was 175 days (IQR: 55.50–706.3 days) after cranioplasty (Table 1).

Surgery-specific characteristics
In 236 of the 254 included patients (92.9%) a post-craniectomy CT-scan was performed. Median defect circumference was 38.5cm (IQR 33.4-41.5cm), ranging from 13.5 to 49.7cm. Median time interval between decompressive craniectomy and cranioplasty was 133 days (IQR: 83.0–199.5 days) (Table 1).

Failure of autologous bone flaps
Of the 254 included patients, the autologous bone flap had to be removed in 52 (20.5%) cases (Table 1). Causes of removal were: infection in 24 (46.2%) cases; resorption in 23 (46.2%); subcutaneous fluid collections in 3 (5.8%); and hemorrhage in two (3.8%) cases. This outcome was not influenced by the year in which the surgical interventions were conducted. Characteristics of patients who suffered flap failure due to infection or resorption are shown in Table 1.
Table 1: Summary of patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>N (%)</th>
<th>Failure N* (%)</th>
<th>Success N (%)</th>
<th>Resorption N (%)</th>
<th>Infection N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>254 (100)</td>
<td>52 (20.5)</td>
<td>202 (79.5)</td>
<td>23 (44.2)</td>
<td>24 (46.2)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Male</td>
<td>130 (51.2)</td>
<td>31 (23.8)</td>
<td>99 (76.2)</td>
<td>15 (65.2)</td>
<td>12 (50.0)</td>
</tr>
<tr>
<td>Age [years, median (IQR)]</td>
<td>45.0 (30.0-53.0)</td>
<td>42.5 (29.0-54.0)</td>
<td>45.0 (32.0-53.0)</td>
<td>29.0 (20.0-54.0)</td>
<td>46.0 (32.5-61.25)</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>37 (14.6)</td>
<td>9 (24.3)</td>
<td>28 (75.7)</td>
<td>3 (13.0)</td>
<td>6 (25.0)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>17 (6.7)</td>
<td>3 (17.6)</td>
<td>14 (82.4)</td>
<td>1 (4.3)</td>
<td>1 (4.2)</td>
</tr>
<tr>
<td>Cardiovascular disease and diabetes</td>
<td>5 (2.0)</td>
<td>1 (20.0)</td>
<td>4 (80.0)</td>
<td>1 (4.3)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>No relevant comorbidity</td>
<td>195 (76.8)</td>
<td>39 (20)</td>
<td>156 (80)</td>
<td>18 (78.3)</td>
<td>17 (70.8)</td>
</tr>
<tr>
<td>Initial diagnosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebrovascular</td>
<td>125 (49.2)</td>
<td>26 (20.8)</td>
<td>99 (79.2)</td>
<td>13 (56.5)</td>
<td>12 (50.0)</td>
</tr>
<tr>
<td>Trauma</td>
<td>93 (36.6)</td>
<td>16 (17.2)</td>
<td>77 (82.8)</td>
<td>8 (34.8)</td>
<td>5 (20.8)</td>
</tr>
<tr>
<td>Tumor</td>
<td>25 (9.8)</td>
<td>9 (36.0)</td>
<td>16 (64.0)</td>
<td>1 (4.3)</td>
<td>7 (29.2)</td>
</tr>
<tr>
<td>Infection</td>
<td>11 (4.3)</td>
<td>1 (9.1)</td>
<td>10 (90.9)</td>
<td>1 (4.3)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Defect circumference [cm, median (IQR)]</td>
<td>38.5 (33.3-41.6)</td>
<td>38.5 (29.2-42.8)</td>
<td>38.4 (34.3-41.3)</td>
<td>397.28 (34.8-44.5)</td>
<td>32.4 (24.6-42.1)</td>
</tr>
<tr>
<td>Time interval between decompressive craniectomy and cranioplasty [days, median (IQR)]</td>
<td>133 (83.0-199.5)</td>
<td>158.5 (90.8-223.5)</td>
<td>125.5 (82.8-191.25)</td>
<td>171 (116.0-224.0)</td>
<td>145.5 (83.3-221.8)</td>
</tr>
<tr>
<td>Length of cranioplasty [minutes; median (IQR)]</td>
<td>110 (79.0-140.0)</td>
<td>114 (83.3-142.5)</td>
<td>108.5 (77.25-140.0)</td>
<td>126.0 (104.0-143.0)</td>
<td>83.5 (55.5-131.3)</td>
</tr>
<tr>
<td>Hospitalization [days; median (IQR)]</td>
<td>112.0 (18.0-533.0)</td>
<td>112.0 (24.3-579.3)</td>
<td>not applicable</td>
<td>618.0 (259.0-884.0)</td>
<td>51.5 (24.25-133.0)</td>
</tr>
<tr>
<td>Follow-up [days; median (IQR)]</td>
<td>175.5 (55.3-1066.3)</td>
<td>713.5 (528.8-1567.3)</td>
<td>97.0 (52.0-406.8)</td>
<td>1229.0 (705.0-1952.0)</td>
<td>424.5 (260.0-1154.3)</td>
</tr>
</tbody>
</table>

*Reasons for failure were resorption, infection, subcutaneous fluid collections and hemorrhage
Overall complication rate
Possible predictive parameters included in the regression model were: gender, age at the time of cranioplasty, co-morbidities (diabetes mellitus, cardiovascular disease, or both), initial indication for decompressive craniectomy (cerebrovascular, trauma, neoplasm, infection), time interval between decompressive craniectomy and cranioplasty, length of cranioplasty procedure (scored from scalp incision to closure), duration of hospitalization after decompressive craniectomy and cranioplasty, failure of cranioplasty, the year of the decompressive craniectomy and cranioplasty, and follow-up duration (calculated from the moment of replacement of the autologous bone flap until the last patient contact before December 2014). Significant independent predictive parameters were: duration of hospitalization after decompressive craniectomy [OR: 1.012 (95%CI: 1.003–1.022); p=0.012] (this OR means that each additional day of hospitalization leads to 1.2% more risk of flap failure); time interval between decompressive craniectomy and cranioplasty [OR: 1.018 (95%CI: 1.004–1.032); p=0.013] (each additional week between decompressive craniectomy and cranioplasty leads to 1.8% higher risk of flap failure); and follow-up duration [OR: 1.034 (95%CI: 1.020–1.047); p<0.001] (i.e., each additional month of follow-up leads to 3.4% higher risk of failure of the bone flap).

Infection
A neoplasm as initial diagnosis occurred more frequently in patients with infection (29.2% vs. 7.8%; RD 21.3%; 95%CI 8.4-38.3%; NNH 5; 95%CI 3-12). The duration of hospitalization after decompressive craniectomy tended to be longer in those with an infected bone flap (means 54 vs. 28 days, MD 26.2 days, 95%CI -8.6 to 60.9 days).

Resorption
Younger patients had a significantly higher risk of bone flap resorption (35 years in the resorption group vs. 43 years in those without resorption; MD 7.7 years, 95%CI 0.8-14.6 years) as well as those with a longer follow-up duration (44 vs. 14 months, MD 29 months, 95%CI 17-42 months). A larger cranial defect size tended to have some influence (mean circumference 39 vs. 37cm, MD 2.4cm, 95% CI -0.43 to 5.2cm).
DISCUSSION

This study shows that cranioplasties with an autologous bone flap fail frequently. One in every five autologous bone flaps eventually had to be removed because of infection, bone flap resorption, subcutaneous fluid collections, or hematoma. Several factors were found to be related to bone flap failure.

Complication rates in cranial reconstructions are high, often resulting in removal of the reconstruction\textsuperscript{2,4,6,11–13,16,18,19,22,27–31}. Current literature reports a median removal rate of 10.4\% (ranging from 0-50\%) for autologous bone flaps and for combined alloplastic cranioplasties 5.1\%\textsuperscript{31}.

Age
Age has been postulated as an influencing factor for the emergence of infections after cranioplasty with autologous bone. Higher metabolic activity in young patients could lead to quicker resorption, but the exact mechanism responsible for this is unclear\textsuperscript{12,13,30,34,35}. Resorption rates of 1\%-50\%\textsuperscript{4,6,12,13,16,22,27,30,36} have been observed for autologous bone flaps, while younger patients may have even higher resorption rates\textsuperscript{12,22,26,30,36,37}. The present study confirmed this association.

Indication for decompressive craniectomy
In this study, an association was found between a neoplasm as the initial diagnosis for decompressive craniectomy and higher infection rates. This patient population did not receive standard radiotherapy as a possible explanation for this association. The current literature also does not offer an explanation, but the slow onset of this disorder likely has a negative impact on recovery, as these patients generally have a suboptimal health condition.
Defect size

Larger craniectomies are considered an essential means of decompression as a life-saving intervention. However, a larger size of the defect tended to foster bone flap resorption. This possible correlation is supported by previous studies, showing that cranial defects above 75 cm\(^2\) were associated with a resorption rate above 60%.\(^1\) Fan et al.\(^3\) reported a significant correlation between bone resorption and cranial defects larger than 100 cm\(^2\). On the other hand, Schoekler and Trummer reported a slightly higher resorption rate in patients with cranial defects over 120 cm\(^2\), but did not find a significant correlation.\(^16\) Similarly, Dünisch et al. did not show a significant association between complications and the size of the defect.\(^22\) Bone graft incorporation depends on the amount of vascularization and resumption of osteogenesis in terms of the formation of bone bridges between the outline of the cranial defect and the reimplanted autologous bone flap.\(^38\) With a larger defect size more revascularization and bone formation needs to occur, which may imply that resorption in larger defects is more likely.

Duration of hospitalization after decompressive craniectomy

In the present study, an association was found between the duration of hospitalization after decompressive craniectomy and the overall complication rate, as well as the infection rate. This may be caused by the overall condition of the patient, comorbidities, newly developed diseases, neurological and surgical outcomes, complications, and rehabilitation period after decompressive craniectomy.\(^1\) To better understand the predictive factors that influence complication rates after cranioplasty, and thereby the length of hospital stay, the surgical outcomes after decompressive craniectomy need to be quantified. Early recovery programs after surgery are known to shorten the length of stay,\(^39\) and may also be applicable in acute situations like cranial decompression surgery to reduce the risk of eventual flap failure.
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Time interval between decompressive craniectomy and cranioplasty
The time interval between decompressive craniectomy and cranioplasty is often considered as a potential risk factor for complications like flap failure,\(^8,21\) which was confirmed in this study. On the other hand, several studies did not find such an association\(^5,22,26\). As a consequence, no consensus on the optimal time interval between decompressive craniectomy and cranioplasty exists. Many studies distinguish an ‘early’ and ‘late’ group, with varying thresholds; 2 weeks, 2 months, 3 months, and even 6 months have been reported.\(^16,21,28,29,35,40,41\) It has been recommended that the cranioplasty be performed at a later stage to avoid operating in a possibly contaminated wound.\(^4\) In contrast, recent findings suggest the cranioplasty may be better performed at an earlier stage to reduce the burden on the patient. Moreover, it may prevent the syndrome of the trephined, and lead to better neurological improvement.\(^4,27,42\)

Schuss et al. showed a significantly lower resorption rate when the autologous bone was reinserted within two months after decompressive craniectomy. Bone flap resorption was observed after about three months after cranioplasty.\(^36\) Brommeland et al. showed a significantly higher resorption rate in delayed cranioplasties.\(^30\) This phenomenon may suggest that if cranioplasty is considered at a later stage in patients who are neurologically unstable, an alloplastic reconstruction may be preferred. Schoekler and Trummer reported a mean interval of 419 days before resorption was observed. However, the timing between decompressive craniectomy and cranioplasty did not significantly influence bone resorption. Still, they recommended the use of an alloplastic cranioplasty when the cranioplasty was planned within two months after the decompressive craniectomy.\(^16\)

A possible reason why resorption is dependent on the time interval between decompressive craniectomy and cranioplasty is the cell viability in the bone graft. The literature reports that autologous bone stored in bone banks at -80°C contains viable cells. It is likely that these cells respond differently to cold storage. If osteocytes in some patients are more vulnerable, this may lead to worse outcomes due to increased resorption.\(^43\) On the other hand, bone flaps kept frozen for 19 months have been shown to maintain the capacity for revascularization.\(^48\)
Follow-up duration
A substantial proportion of the autologous bone flaps fail in time. Hence, patients with a long-life expectancy may be better served with an alloplastic cranioplasty. In the long run, when resorption of an autologous bone flap occurs, the protection of the brain is diminished, fracture is more likely, and esthetics will be compromised due to atmospheric air pressure. It may therefore be advisable to develop a protocol to extend the follow-up period. This may result in a more timely intervention when there are clinical signs for failure of the bone flap, which may reduce definitive bone flap failures in time.

Limitations of this study
The retrospective nature of this study implies a risk of reporting bias, as it was limited to the available information documented in patient charts, including whether or not antibiotics were given. This led to patient exclusions because of unknown follow-up data, which is likely to occur if the follow-up period was uneventful and patients would have no need to visit their surgeon. Thus, the present findings about failure rates might be slightly exaggerated. In addition, the association between bone flap failure and various parameters was statistically significant but with a limited clinical relevance due to the relatively small number of patients available. The impact of these parameters on clinical practice deserves further investigation.

Second, in this study resorption and infection were defined clinically in case of flap removal, although this was not verified microbiologically. However, we think this would not have influenced the results of this study substantially.

Third, the circumference rather than the surface area of the defect was used for the measurements. Because the skull has convex and concave areas, the measurement of the surface area of the defect is complicated. However, the measured circumference is likely to give a reliable indication of the defect in the cranium of the patient.
Fourth, this study only included autologous bone that was stored in the freezer at -80°C. However, other options for bone storage are mentioned in the literature. Corliss showed no significant differences between cryopreservation and storage in an abdominal pocket for resorption (9.7 vs 7.7), infection (7.3 vs 7.1) or reoperations (15.9 vs 7.6)\textsuperscript{44}. Another study showed a resorption rate of 20% after bone flap sterilization and storage in a refrigerator at 8°C\textsuperscript{6}. Nowadays, numerous alloplastic materials have been developed for cranioplasties, each with their own benefits and potential harms. The most frequently reported materials are poly(methyl methacrylate) (PMMA), poly (ether ether ketone) (PEEK), titanium, hydroxyapatite. However, there is still no consensus on the optimal material for cranial reconstruction\textsuperscript{31}.

CONCLUSION

The risk of autologous bone flap failure in patients who underwent decompressive craniectomy is considerable, especially in those operated for a neoplasm. Patients with a longer hospitalization time after decompressive craniectomy may benefit from an early recovery program after surgery to eventually reduce failure of the cranioplasty, or by the use of an alloplastic material for cranial reconstruction. This also holds for patients with a large cranial defect and those with a longer life expectancy. There is still no consensus about the time interval between decompressive craniectomy and cranioplasty. A randomized trial could help make an evidence-based decision when to proceed with the cranioplasty. Finally a standard follow-up protocol may improve early detection and reduce the risk of failure of an autologous bone flap.
REFERENCES

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