Postcranioplasty seizures following decompressive craniectomy and seizure prophylaxis: a retrospective analysis at a single institution

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OBJECTIVE Cranioplasty is a relatively simple and less invasive intervention, but it is associated with a high incidence of postoperative seizures. The incidence of, and the risk factors for, such seizures and the effect of prophylactic anti-epileptic drugs (AEDs) have not been well studied. The authors' aim was to evaluate the risk factors that predispose patients to postcranioplasty seizures and to examine the role of seizure prophylaxis in cranioplasty.

METHODS The records of patients who had undergone cranioplasty at the authors' medical center between 2009 and 2014 with at least 2 years of follow-up were retrospectively reviewed. Demographic and clinical characteristics, the occurrence of postoperative seizures, and postoperative complications were analyzed.

RESULTS Among the 583 patients eligible for inclusion in the study, 247 had preexisting seizures or used AEDs before the cranioplasty and 336 had no seizures prior to cranioplasty. Of these 336 patients, 89 (26.5%) had new-onset seizures following cranioplasty. Prophylactic AEDs were administered to 56 patients for 1 week after cranioplasty. No early seizures occurred in these patients, and this finding was statistically significant ($p = 0.012$). Liver cirrhosis, intraoperative blood loss, and shunt-dependent hydrocephalus were risk factors for postcranioplasty seizures in the multivariable analysis.

CONCLUSIONS Cranioplasty is associated with a high incidence of postoperative seizures. The prophylactic use of AEDs can reduce the occurrence of early seizures.

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KEYWORDS cranioplasty; craniectomy; seizure; seizure prophylaxis; complication; surgical technique

CRANIOPLASTY, the placement of a bone flap or prosthesis to repair a defect in the skull, is a surgical procedure usually performed in patients who have undergone decompressive craniectomy (DC) due to poor control of elevated intracranial pressure following traumatic brain injury (TBI) or stroke. Though it is a relatively simple procedure, many complications, such as hemorrhage, infection, and bone necrosis, have been reported.^{11,14,22,27} In addition, seizures are common after cranioplasty and are associated with poor outcomes; however, the risk factors for, and the incidence of, such seizures have not been well described. Moreover, there are few reports about the effect of antiepileptic drugs (AEDs) for seizure prophylaxis.¹⁵ Our aim was to evaluate the risk factors that

predispose patients to postcranioplasty seizures and to examine the role of seizure prophylaxis in cranioplasty.

Methods

Study Design

The records of patients who had undergone cranioplasty at a single medical center during the period from January 2009 to December 2014 and who had at least 2 years of follow-up were retrospectively reviewed. The study included all patients who had initially undergone DC for brain swelling due to TBI, hemorrhagic or ischemic stroke, or brain tumor or abscess. To standardize the baseline risks and pathological entities, the study excluded patients

ABBREVIATIONS AED = antiepileptic drug; DC = decompressive craniectomy; PMMA = polymethylmethacrylate; TBI = traumatic brain injury.

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who had undergone craniectomy for bone flap infections following craniotomy for all causes; neoplastic etiologies that involved the skull, such as meningioma and skull tumors; and cranioplasty for traumatic compound fractures. The institutional review board of Chang Gung Memorial Hospital approved the study.

Study Variables

Patient demographic data including age and sex were collected, as were data on the following medical comorbidities: hypertension, diabetes mellitus, end-stage renal disease, liver cirrhosis, and hydrocephalus before cranioplasty (permanent CSF shunt prior to and at the time of cranioplasty). Data on all operations and the duration of follow-up were recorded. Details of the initial DC were reviewed to identify the initial pathology. Extensive DC of at least 12 × 14 cm along with dural augmentation was performed by experienced surgeons. A synthetic, suturable, nonabsorbable dural substitute (Neuro-Patch, Aesculap) was used as an artificial dural barrier. The type of material used to reconstruct the cranial defect was classified as autologous bone, 3D polymethylmethacrylate (PMMA; constructed with 3D printing technology), or titanium mesh (Biomesh, Bioplate Inc.; constructed with 3D printing technology). Blood loss during cranioplasty, repeat craniotomy before cranioplasty, and repeat cranioplasty were also recorded and analyzed. Complications related to cranioplasty were identified as postoperative intracranial hematoma (including subdural, epidural, and intraparenchymal hematoma) requiring reoperation, infection needing surgical debridement at the surgical site or abscess and empyema requiring reoperation, and hydrocephalus that developed and required a permanent CSF shunt after cranioplasty. All surgical procedures were performed by 10 neurosurgeons, each with over 5 years' experience performing craniectomy and cranioplasty. Two of the surgeons administered prophylactic AEDs for 1 week after cranioplasty.

A postoperative seizure was defined as any seizure that occurred after cranioplasty (early: ≤ 1 week after operation, late: > 1 week after operation).³ All patients who had undergone cranioplasty were divided into two groups: those with preexisting seizures before cranioplasty, and those with no seizures before cranioplasty. Seizure prophylaxis was defined as the prophylactic use of an AED after cranioplasty in patients who had no seizures before cranioplasty, and the drug was discontinued 1 week postoperatively if no seizures developed. Phenytoin or sodium valproate is the primary AED used at our center, and levetiracetam is only used when liver function impairment is identified prior to surgery. The dosage of AED for seizure prophylaxis is similar to that used in cases of traumatic head injury. Phenytoin was administered at a dose of 15–20 mg/kg by slow intravenous infusion before closure of the cranioplasty wound, followed by a 100-mg maintenance dose 3–4 times a day for 3 days, and then changed to 300 mg orally once a day for the following 4 days. Sodium valproate was administered at a dose of 10–15 mg/kg by slow intravenous infusion before wound closure, then 10–60 mg/kg daily as a maintenance dose for 3 days, and then an oral form for the following 4 days. Levetiracetam

was administered at a dose of 500 mg by slow intravenous infusion before wound closure, and then a dose of 500 mg twice daily.

Statistical Analysis

Baseline characteristics of the patients with and without seizures were compared using Fisher's exact test for categorical variables or a t-test for continuous variables (univariable analyses). The variables with a value of $p < 0.2$ in the univariable analyses were input into a multivariable logistic regression model with backward selection. Finally, using Fisher's exact test, we compared the proportion of seizures in patients with and without AED use. A value of $p < 0.05$ was considered statistically significant. Data analyses were conducted using SPSS version 22 (IBM Corp.).

Results

Baseline Characteristics

A total of 583 patients were included in this analysis. Of these patients, 247 had preexisting seizures or used AEDs before the cranioplasty and 336 patients had no seizures prior to the cranioplasty. Demographic and clinical data on the 336 patients without preexisting seizures before the cranioplasty are summarized in Table 1. Of these 336 patients, 220 (65.5%) had traumatic head injuries; 47 (14.0%) had cerebral infarctions; 32 (9.5%) had spontaneous intracerebral hemorrhage due to hypertension, arteriovascular malformations, aneurysms, or other vascular conditions; 28 (8.3%) had brain tumors; and 9 (2.7%) had spontaneous intracerebral infections (empyema or abscess). A total of 222 (66.1%) patients received autologous bone flap reinsertion, 72 (21.4%) received 3D PMMA, and 42 (12.5%) received a titanium implant. Eighty-two patients had permanent hydrocephalus before cranioplasty. After cranioplasty, 20 (6.0%) patients had postoperative infection and needed a repeat craniotomy, 5 (1.5%) had postoperative acute hemorrhage, and 31 (9.2%) had delayed hydrocephalus.

Postcranioplasty Seizures

Eighty-nine (26.5%) patients experienced new-onset seizures. Univariable analyses showed that the initial reason for the DC, intraoperative blood loss, postoperative hemorrhage, and hydrocephalus before or after cranioplasty were associated with postcranioplasty seizures. Table 2 demonstrates the results of the multivariable analysis for new-onset seizures. Cirrhosis, intraoperative blood loss, and hydrocephalus were found to be risk factors for postcranioplasty seizures. Of the 336 patients without preexisting seizures, prophylactic AEDs were administered to 56 (16.7%) for 1 week after cranioplasty. No early seizures occurred in these 56 patients. Phenytoin, sodium valproate, and levetiracetam were used in 37, 16, and 3 of the patients, respectively. The effect of prophylactic AEDs for new-onset postcranioplasty seizures is summarized in Table 3. Antiepileptic drug use showed statistical significance ($p = 0.012$) toward protection against early seizures after cranioplasty. According to our results, the number needed to treat (NTT) is 8.9. That means that 8.9 seizures (early seizure) on average can be prevented because of the administration of AEDs. All drugs used were effective.

TABLE 1. Characteristics of 336 patients without seizures before cranioplasty

Variable	New-Onset Szs	No Szs	p Value
No. of patients	89 (26.5%)	247 (73.5%)	
Age in yrs	44.7 ± 17.5	44.6 ± 18.4	0.977
Sex			1.000
F	29 (32.6%)	83 (33.6%)	
M	60 (67.4%)	164 (66.4%)	
Initial reason for DC			0.019
ICH & vascular lesions	11 (12.4%)	21 (8.5%)	
Infarction	9 (10.1%)	38 (15.4%)	
Infection	3 (3.4%)	6 (2.4%)	
Trauma	63 (70.8%)	157 (63.6%)	
Tumor	3 (3.4%)	25 (10.1%)*	
Interval btwn 2 procedures in days	245.5 ± 491.9	335.6 ± 784.7	0.374
Bone material			0.065
3D PMMA	12 (13.5%)	60 (24.3%)	
Autologous	66 (74.2%)	156 (63.2%)	
Titanium	11 (12.4%)	31 (12.6%)	
End-stage renal disease	1 (1.1%)	1 (0.4%)	0.435
Liver cirrhosis	4 (4.5%)	2 (0.8%)	0.100
Impaired liver function	11 (12.4%)	22 (8.9%)	0.519
Coagulopathy	6 (6.7%)	8 (3.2%)	0.119
Diabetes mellitus	14 (15.7%)	31 (12.6%)	0.546
Hypertension	24 (27.0%)	69 (27.9%)	1.000
Intraop blood loss (ml)	245.9 ± 212.1	196.4 ± 167.6	0.0497
Postop hemorrhage†	5 (5.6%)	0 (0.0)	0.001
Postop infection	5 (5.6%)	15 (6.1%)	0.375
No. of previous ops	1.7 ± 1.0	1.8 ± 1.4	0.344
Repeat cranioplasty	9 (10.1%)	23 (9.3%)	0.819
Hydrocephalus before cranioplasty	32 (36.0%)	50 (20.2%)	0.014
Hydrocephalus after cranioplasty	14 (15.7%)	17 (6.9%)	0.028

ICH = intracerebral hemorrhage; Sz = seizure.

Values expressed as the mean ± standard deviation or as the frequency (percent), unless indicated otherwise.

* Indicates $p < 0.05$ in the Bonferroni-adjusted post hoc comparison.

† Hemorrhage includes epidural, subdural, and intraparenchymal hematoma requiring reoperation.

tive for seizure prophylaxis. No allergic or drug-related complications occurred in these 56 patients. After 1 week, AEDs were discontinued in all patients as no early seizures occurred. Sixteen (28.6%) of the 56 patients had late seizures after cranioplasty. Overall, late-onset seizures occurred in 19% (64/336) of the patients after cranioplasty. Eight (2.4%) of the 336 patients suffered from new-onset seizures at 1 year postoperatively. The AEDs showed no protective effect against late seizures.

In the 247 patients who had preexisting seizures before cranioplasty, 106 (42.9%) had frequent postoperative seizures and required an increased dosage of the AEDs

TABLE 2. Multivariable analysis for new-onset seizures

Variable	OR	95% CI	p Value
Liver cirrhosis	7.27	1.14–46.58	0.036
Intraop blood loss, per 10 ml	1.02	1.002–1.033	0.024
Hydrocephalus before cranioplasty	3.13	1.64–5.96	0.001
Hydrocephalus after cranioplasty	4.52	1.84–11.12	0.001

they were taking or the addition of new AEDs for seizure control. Only 57.1% patients who had preexisting seizures remained seizure free or had stable seizure control 2 years after cranioplasty.

Discussion

Cranioplasty is not merely a cosmetic operation, but provides protection to the intracranial contents from further injury and improves cerebral blood flow and neurological function.^{1,13,18,19,26} However, postoperative seizures can lead to serious secondary complications, such as increased intracranial pressure and trauma from falling, resulting in further morbidity and even death. Cranioplasty after DC has been reported to be associated with a relatively high complication rate (16.4%–34%) as compared to the rate after standard neurosurgical procedures (2%–5%).⁸ The reported incidence of postcranioplasty seizures varies from 8% to 33%.^{10,14,22,27} Our study showed a 7.4% (25/336) early seizure rate and a new-onset seizure rate of 26.5% (89/336) in the long-term follow-up. In the patients with preexisting seizures before cranioplasty, the rate of postoperative seizures reached 42.9%. Therefore, cranioplasty is associated with a relatively high incidence of postoperative seizures.

Mechanisms of Postcranioplasty Seizures

Seizures after cranioplasty may be the result of either the underlying brain condition or the cranioplasty procedure itself. In our study, 42.9% of patients with preexisting seizures before cranioplasty had postoperative seizures, which suggests that the underlying brain pathology affects the occurrence of seizures. The pathophysiology of early and late seizures is slightly different. Diffuse brain edema and ischemia lead to the release of excitatory cellular components and toxic mediators causing early seizures.¹² Cranioplasty is considered an extradural procedure, and the manipulation of brain tissue during dissection of the extradural plane is unavoidable, which can result in brain edema. The dissection will also reduce focal cerebral blood flow because of the disconnection between the scalp and dura mater, which can cause relative ischemia in the underlying cortex. Moreover, brain tissue is further manipulated to facilitate the new contour of the bone flap after cranioplasty. These manipulations may precipitate seizure activity in already susceptible brain tissue and have been postulated to be mechanisms for postcranioplasty seizures.^{14,16} Late-onset seizures may be caused by a cascade of further events followed by hemorrhage, hemolysis, iron compound exportation, free radical formation, peroxidation, and cell death resulting in damage to the brain cortex and the formation of epileptogenic foci.^{6,21}

TABLE 3. Prophylactic AED use in patients without preexisting seizures

Variable	AEDs (n=56)	No AEDs (n=280)	p Value
New-onset Sz (n=89)			0.741
No	40 (71.4)	207 (73.9)	
Yes	16 (28.6)	73 (26.1)	
Early Sz (n=25)			0.012
No	56 (100.0)	255 (91.1)	
Yes	0 (0.0)	25 (8.9)	
Late Sz (n=64)			0.061
No	40 (71.4)	232 (82.9)	
Yes	16 (28.6)	48 (17.1)	

Early Sz = seizure onset $\leq$ 7 days after cranioplasty; late Sz = seizure onset $>$ 7 days after cranioplasty; n = total number of patients.

Boldface type indicates statistical significance.

Although the operation itself can also produce free radicals, disturb the ionic balance, and involve manipulation of the cerebral parenchyma, the cause of late-onset seizures is likely multifactorial.^{14,27}

Prophylaxis Against Postcranioplasty Seizures

A course of seizure prophylaxis for a week has only been well established for posttraumatic head injuries.^{2,3,20} The incidence of postcranioplasty seizures is similar to, or even higher than, that seen with severe head injury.^{3,7} Therefore, the use of prophylactic AEDs should be considered for patients after cranioplasty. In this study, although the number of patients who received prophylactic AEDs for 1 week was only 56, none of them had early seizures. The effect of early seizure prophylactics is obvious. There were no immediate or delayed adverse effects in the 56 patients, such as an allergic skin reaction, liver dysfunction, or impaired cognitive function. Phenytoin, sodium valproate, and levetiracetam are commonly used drugs, and all are effective at preventing post-TBI and postcraniotomy seizures.^{2,3,20} Although the use of levetiracetam appears to be increasing for seizure prophylaxis, phenytoin (37/56 patients) is still the first choice at our center and is recommended to decrease the incidence of early posttraumatic seizures.³

Risk Factors for Postcranioplasty Seizures

Risk factors for postcranioplasty seizures have been reported to be TBI, hemorrhagic stroke, postoperative infection, postoperative hemorrhage, patient sex, and neurological deficits before operation.^{14,22,27} In our study, we found that intraoperative blood loss, postoperative hemorrhage, and hydrocephalus before or after cranioplasty were associated with seizures. After multivariable analysis, cirrhosis, intraoperative blood loss, and shunt-dependent hydrocephalus were predictors of postcranioplasty seizures. As shown in Table 1, the presence of a brain tumor reached statistical significance ($p < 0.05$) in the univariable analysis but was not significant in the multivariable analysis. Brain tumors were present in 28 patients (8.3%) in our study, but only 3 of these patients had new-onset seizures. It is likely that after tumor removal in the initial operation, the main seizure focus was removed. When these patients

underwent cranioplasty, the rate of postoperative seizures was less than that associated with other etiologies. A prior randomized trial has suggested that brain tumor surgery itself does not have an influence on postoperative seizure and that prophylactic AEDs are unnecessary.²⁴ In our study, only 10 patients had cirrhosis, and 4 of those with preexisting seizures before cranioplasty had more frequent seizures postoperatively. On the other hand, 4 of the 6 patients with cirrhosis and no seizures before cranioplasty had new-onset seizures. Thus, it seems advisable to carefully observe for new-onset or worsening seizures after cranioplasty in patients with cirrhosis. In such patients, seizures may result directly from the cranioplasty or from cirrhosis-related hepatic encephalopathy.⁴ Intraoperative blood loss and postoperative hemorrhage imply more brain manipulation and the new accumulation of hematoma after cranioplasty and re-switch on the process of hemolysis, iron exploration, and free radical releasing. These factors can lead to new-onset seizures after cranioplasty.

Our study showed that patients with hydrocephalus before or after cranioplasty have a higher risk of postoperative seizures. Hydrocephalus is well documented as a common complication after DC.^{9,16,25} When hydrocephalus develops in a patient after craniectomy, the brain may progressively bulge at the craniectomy site and a permanent shunt may be required. Cranioplasty has also been reported to contribute to the development of persistent hydrocephalus.^{17,23,27} Cranioplasty can affect the cerebral perfusion pressure and change the intracranial pressure.^{5,9,10} Performing cranioplasty in a sunken or bulging brain can create negative or positive pressure, respectively, and thus alter the intracranial pressure. That is why, clinically, adjusting the ventriculoperitoneal (VP) shunt pressure before cranioplasty, undergoing VP shunt insertion simultaneously with cranioplasty, or developing complications such as subdural fluid collection or subdural hematoma after cranioplasty occurs very frequently. Such brain pressure changes and complications could be caused or aggravated by CSF drainage and induce a seizure.^{9,22,23,27} We were unable to determine whether hydrocephalus was a direct complication of the primary brain injury, the craniectomy, or the cranioplasty. Thus, we suggest close surveillance for the development of hydrocephalus following cranioplasty.

Limitations and Further Study

The strength of this study is the long-term follow-up, the large sample size, and the single-center results without patient selection bias. However, the limitations of this study are the retrospective design and small number of patients who received prophylactic AEDs. In this study, only two attending neurosurgeons administered routine prophylactic AEDs for cranioplasty. Previous authors have suggested a new protocol for seizure prophylaxis based on their study results;^{22,27} however, seizure prophylaxis for cranioplasty is still not a common practice.

Conclusions

Cranioplasty is associated with a relatively high incidence of postoperative seizures. Patients who have underlying cirrhosis, more intraoperative blood loss, or shunt-

dependent hydrocephalus are at greater risk for postcranioplasty seizures. Prophylactic use of AEDs for 1 week after cranioplasty can reduce the occurrence of early seizures. On average, the number needed to treat is 8.9 seizures (early seizure), which can be prevented with the administration of AEDs.

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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: Tu, Chen. Acquisition of data: Chen. Analysis and interpretation of data: Tu, Yeap, Chen, ZH Liu. Drafting the article: Yeap, Chen. Critically revising the article: Tu, Yeap, Chen. Reviewed submitted version of manuscript: Tu, Chen, Liu, Hsieh. Approved the final version of the manuscript on behalf of all authors: Tu. Administrative/technical/material support: Chen, ZH Liu, Hsieh, Lee, YT Liu, Wang, Huang, Wei, Wu. Study supervision: Tu, ZH Liu, Wei, Wu.

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