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Risk factors for seizures after cranioplasty

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ABSTRACT

Purpose: Cranioplasty can improve a patient's psychosocial and cognitive functions after decompressive craniectomy, however seizures are a common complication after cranioplasty. The risk factors for early and late seizures after cranioplasty are unclear. This study is to evaluate the risk factors for early and late seizure after cranioplasty.

Methods: Two hundred and thirty-eight patients who received cranioplasty following craniectomy between January 2012 and December 2014 were included in this study. The risk factors of the patients with early and late post-cranioplasty seizures were compared to those with no post-cranioplasty seizures.

Results: Seizures (73/238, 30.3%) were the most common complication after cranioplasty. Of these 73 patients, 17 (7.1%) had early post-cranioplasty seizures and 56 (23.5%) had late post-cranioplasty seizures. Early post-cranioplasty seizures were related to a longer interval between craniectomy and cranioplasty ($P = 0.006$), artificial materials ($P < 0.001$), and patients with late post-craniectomy seizures ($P = 0.001$). Late post-cranioplasty seizures were related to the presence of neurological deficits ($P = 0.042$). After stepwise logistic regression analysis, a longer interval between craniectomy and cranioplasty ($P = 0.012$; OR: 1.004, 95% CI: 1.001–1.007) and late post-craniectomy seizures ($P = 0.033$; OR: 4.335, 95% CI: 1.127–16.675) were independently associated with early post-cranioplasty seizures.

Conclusion: Delayed cranioplasty procedures and seizures before cranioplasty were significantly associated with early post-cranioplasty seizures. Further studies are warranted to investigate whether early surgery after craniectomy can reduce the risk of early post-cranioplasty seizures.

1. Introduction

Decompressive craniectomy is a life-saving procedure that can alleviate intractable raised intracranial pressure caused by various brain injuries including trauma, hemorrhage, or large cerebral infarctions. Seizures have been reported in 3–92% of patients who receive craniectomy [1], and their occurrence has been associated with multiple underlying etiologies. Cranioplasty is an elective procedure for skull reconstruction after decompressive craniectomy, and it has been shown to improve both psychosocial and cognitive functions [2–5]. Various complications following cranioplasty have been reported including seizures, hydrocephalus, hematoma, infection, implant loosening, and death [6], with rates of seizures after cranioplasty ranging from 2.7 to 29.0% [7,8]. However, few studies have explored the risk factors for post-cranioplasty seizures [9,10]. In this study, we aimed to analyze the risk factors associated with the occurrence of post-cranioplasty seizures, with particular emphasis on the existence of pre-cranioplasty seizures or not.

2. Material and methods

2.1. Study design

Adult patients (age: 15–85 years) who received cranioplasty between 2012–2014 at the Department of Neurosurgery of Kaohsiung Chang Gung Memorial Hospital were enrolled in this observational study. We excluded patients who had previously undergone cranioplasty for facial reconstruction, craniectomy and cranioplasty in one procedure, or cranioplasty at a different institution. The study protocol was approved by the local Institutional Review Committee on Human

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Research. A neurosurgeon obtained clinical information by reviewing medical charts. A structured questionnaire was used to record the demographic data including age, sex, etiology of craniectomy, interval between craniectomy and cranioplasty, lateralization of cranioplasty, the type of cranioplasty material, pre-cranioplasty hydrocephalus, neurological deficits before cranioplasty, past medical history, onset of post-cranioplasty seizures, and other complications.

2.2. Clinical assessment

Early post-cranioplasty seizures were defined as seizures occurring within 7 days after the operation. Seizures occurring on day 8 or later were classified as late post-cranioplasty seizures. [9,11] Patients with a history of seizures before cranioplasty were further classified according to the timing of seizure onset and craniectomy as follows: early post-craniectomy seizures (within 7 days after craniectomy), and late post-craniectomy seizures ($> = 8$ days after craniectomy). None of the patients had seizures before craniectomy. Unprovoked seizures were defined as late post-craniectomy and -cranioplasty seizures. Pre-cranioplasty hydrocephalus was defined as the insertion of a ventriculoperitoneal shunt before or at the same time as cranioplasty. Patients who had cognitive impairment, aphasia, or focal motor deficits were considered as having neurological deficits. The prophylactic antiepileptic drug was defined as administered drugs for one week after craniectomy or cranioplasty. The cranioplasty material included autologous bone, para-methylamphetamine, and a computer-aided design with titanium. The autologous bone flaps were sealed in sterilized plastic bags and stored in a deep freezer at −86 °C after craniectomy. Post-cranioplasty complications were recorded as follows: hydrocephalus, seizures, hematoma requiring reoperation, surgical site infection, poor wound healing, implant loosening, and death [6].

2.3. Statistical analysis

Outcome measures included the presence of early or late post-cranioplasty seizures. Categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate, and continuous variables were assessed using the Mann-Whitney U test. Data were expressed as median (inter-quartile range [IQR]), and statistical significance was set at $p < 0.05$. Stepwise logistic regression analysis was used to evaluate significant variables ($p < 0.05$) among the patients with early, late, and no post-cranioplasty seizures.

The Kaplan-Meier method was used to estimate the cumulative risk of post-cranioplasty late seizures. For continuous variables, receiver operating characteristic curve analysis was used to estimate optimal cut-off values by maximizing the sum of sensitivity and specificity. All statistical analyses were conducted using SPSS software version 12.0 (Chicago, IL, USA).

3. Results

3.1. Baseline characteristics of the study patients

The data of 238 patients who underwent craniectomy and subsequent cranioplasty were collected and analyzed (Fig. 1). The characteristics of the patients with cranioplasty are listed in Table 1, including 160 (67.2%) males and 78 (32.8%) females. The median age at cranioplasty was 51.9 years (range: 15–85 years). The median time interval between craniectomy and cranioplasty was 52 days, and the median follow-up was 24.3 months. The etiologies for initial decompressive craniectomy were as follows: 152 patients (63.9%) with a traumatic brain injury, 50 (21.0%) with a hemorrhagic stroke, 16 (6.7%) with an ischemic stroke, 14 (5.9%) with a brain tumor, and six (2.5%) with a brain abscess. The most common cranioplasty material was autologous bone (89.5%). Fifty patients (21.0%) had pre-cranioplasty seizures, including 31 (13.0%) with early post-craniectomy seizures and 19 (8.0%) with late post-craniectomy seizures. With regards to the cranioplasty procedure, seizures (30.3%) were the most common complication. Seventeen (7.1%) patients had early post-cranioplasty seizures and 56 (23.5%) had late post-cranioplasty seizures, including one patient with both early and late seizures.

3.2. Risk factors associated with early post-cranioplasty seizures

We further investigated the risk factors for the patients who developed post-cranioplasty seizures (Table 2). The risk factors for early post-cranioplasty seizures were a longer interval between craniectomy and cranioplasty ($P = 0.006$), artificial materials ($P < 0.001$), and patients with late post-craniectomy seizures ($P = 0.001$). After stepwise logistic regression analysis, a longer interval between craniectomy and cranioplasty ($P = 0.012$; OR: 1.004, 95% CI: 1.001–1.007) and late post-craniectomy seizures ($P = 0.033$; OR: 4.335, 95% CI: 1.127–16.675) were independently associated with early post-cranioplasty seizures. The cut-off point of the interval between craniectomy and cranioplasty according to receiver operating characteristic curve analysis was 88.5 days (area under the curve 0.717; 95% CI 0.565–0.868; $P = 0.003$) with 58.8% sensitivity and 77.8% specificity to predict early post-cranioplasty seizures (Fig. 2).

3.3. Risk factors associated with late post-cranioplasty seizures

The presence of neurological deficits ($P = 0.042$) was the only risk factor for late post-cranioplasty seizures. Kaplan-Meier curves showed the relationship between neurological deficits and post-cranioplasty seizures (Fig. 3). The 3-year late post-cranioplasty rate was 20.3% in the patients without neurological deficits, and 36.6% in those with neurological deficits (log-rank $P = 0.009$).

3.4. Risk factors of post-cranioplasty seizures in patients without post-craniectomy seizures

Among our study group, 188 (79.0%) patients had no seizures before cranioplasty. After cranioplasty, 11 (5.9%) and 41 (21.8%) developed new onset early and late post-cranioplasty seizure, respectively. The risk factors for early post-cranioplasty seizures were longer interval between craniectomy and cranioplasty ($P = 0.01$) and artificial materials ($P = 0.024$). Late post-cranioplasty seizures was associated with bilateral cranioplasty ($P = 0.013$) (Table 3).

3.5. Risk factors of post-cranioplasty seizures in patients with post-craniectomy seizures

In patients ($n = 50$) who developed seizures before cranioplasty (including 31 early and 19 late post-craniectomy seizures), there were 6 (15%) had early post-cranioplasty seizures and 15 (37.5%) had late post-cranioplasty seizures ($p = 0.075$, respectively compared to no post-craniectomy seizures). The risk of early post-cranioplasty seizures were artificial materials ($P = 0.019$), late post-craniectomy seizures ($P = 0.028$), and pre-cranioplasty hydrocephalus ($P = 0.041$). Male sex ($P = 0.017$) was a risk factor for late post-cranioplasty seizures (Table 4).

4. Discussion

In this study, 30.3% of the cranioplasty patients had post-operative seizures, which was the most common complication of the procedure. Among these patients, early seizures occurred in 7.1%, and 23.5% patients had late seizures. We identified different risk factors associated with different phases of post-cranioplasty seizures. The interval between craniectomy and cranioplasty, and the presence of late seizures after previous craniectomy were associated with early post-cranioplasty seizures, while the presence of neurological deficits was associated with

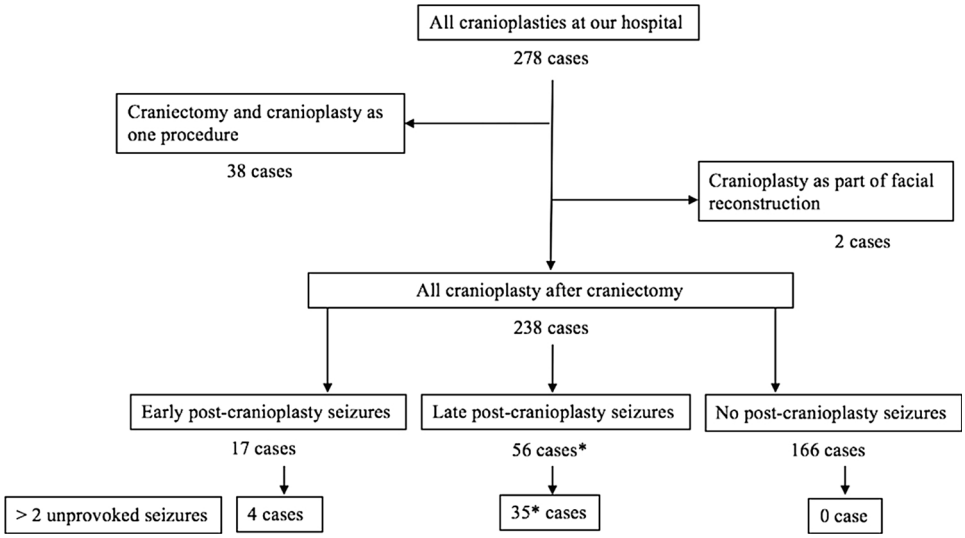

Fig. 1. The flow chart of the patients who underwent cranioplasty who were included and excluded from analysis.
*One patient had both early and late post-cranioplasty seizures.

Table 1
The characteristics of the patients who underwent cranioplasty.

Patient demographics	
Total patients	238
Male/Female (%)	160 (67.2%)/78 (32.8%)
Median age, years (± SD)	51.9 (± 18.2)
Time from craniectomy to cranioplasty (IQR, days)	52 (32, 85)
Median duration of follow-up (IQR, months)	24.3 (10.5, 33.1)
Reason for craniectomy (%)	
Traumatic brain injury	152 (63.9%)
Hemorrhagic stroke	50 (21.0%)
Ischemic stroke	16 (6.7%)
Tumor	14 (5.9%)
Brain abscess	6 (2.5%)
Replacement material (%)	
Autologous	213 (89.5%)
PMMA	8 (3.4%)
CAD (titanium)	17 (7.1%)
Pre-cranioplasty seizure	
Early post-craniectomy	31 (13.0%)
Late post-craniectomy	19 (8.0%)
Complications (%)	
Seizures	
Early post-cranioplasty	17 (7.1%)*
Late post-cranioplasty	56 (23.5%)
Hydrocephalus[#]	26 (10.9%)
Hematoma	5 (2.1%)
Surgical site infection	12 (5.0%)
Wound healing disturbance	4 (1.7%)
Implant loosening	2 (0.8%)
Overall	83 (34.9%)

Abbreviations: PMMApara-methylamphetamine; CADcomputer-aided design; IQRinter-quartile range; SDstandard deviation; [#]; Hydrocephalus occurred after cranioplasty; *One patient had both early and late post-cranioplasty seizures.

late post-cranioplasty seizures.

The prevalence of post-cranioplasty seizures has been reported to range from 3.35% to 29% in previous studies [6,8,9,12,13]. In the current study, nearly one third of the patients who underwent cranioplasty had seizures, and 7.1% of all cranioplasty patients had early onset seizures. This is slightly higher compared to previous studies which reported rates ranging from 3.8% to 5.1% [9,10]. This is probably due to we did not exclude patients who had seizures before cranioplasty compared to other studies. We also found that the patients who had late post-craniectomy seizures were at higher risk of recurrent seizures if they received a second operation such as cranioplasty. This may be because they had a lower seizure threshold that made them prone to recurrence under physiological stress caused by the surgical procedures.

The timing of cranioplasty is one of the most controversial topics in cranioplasty [14,15]. Recent studies have reported no difference in the incidence of infection between early cranioplasties and cranioplasties performed after 6 months [14,16–19]. In addition, some studies have shown that patients who underwent early cranioplasties had better functional outcomes [7,20,21]. However, no previous study has focused on the timing of cranioplasty and the occurrence of post-cranioplasty seizures. In this study, we found that a longer interval between craniectomy and cranioplasty was an independent risk factor for early post-cranioplasty seizures. Surgery may result in the production of free radicals, disturb ionic balance, and affect cerebral parenchyma, all of which have been proposed as mechanisms for the occurrence of post-operative seizures [22–24]. However, cranioplasty is an extradural procedure that usually involves minimal manipulation of brain tissue during dissection of the extradural plane. It is possible that a longer duration between craniectomy and cranioplasty may increase the difficulty in separating the epidural area and brain tissue due to wound adhesion. Therefore, delayed cranioplasty may be more likely to influence the brain parenchyma due to the necessity for more manipulations [9,23,24].

The presence of neurological deficits was the only risk factor for the development of late post-cranioplasty seizures in our cohort. A previous study identified that traumatic brain injury, hemorrhagic stroke, and neurologic deficits before cranioplasty were risk factors for late post-cranioplasty seizures [9]. Although the etiology of craniectomy did not increase the risk in our study, the presence of neurological deficits, which represents the severity of brain parenchyma damage, was associated with late post-cranioplasty seizures. This is in accordance with the concept that focal tissue destruction is the most important factor in predicting the development of late seizures [25,26]. The underlying mechanism of late post-cranioplasty seizures is probably the same as late post-craniectomy seizures, which is the extension of the consequence of the initial brain insults.

Subgroup analysis showed that patients who had seizures before cranioplasty had higher rate of both early and late post-cranioplasty seizures compared to patients without seizures before cranioplasty. Particularly, patients with late post-craniectomy seizures are more likely to have early pre-cranioplasty seizures. Although cranioplasty is a less invasive procedure, our study suggests that patients who developed seizures before the procedure are also more likely to develop early

Table 2
Risk factors for post-cranioplasty seizures.

	Early post-cranioplasty seizures n = 17	*p* value$^{\Delta}$	Late post-cranioplasty seizures n = 56*	*p* value$^{\Delta}$	No post-cranioplasty seizures n = 166
Median age (years, IQR)	54 (45.5, 73)	0.435	52 (39.75, 63.75)	0.915	51.5 (36, 67)
Male/Female (%)	11 (4.6%)/6 (2.5%)	0.984	43 (18.0%)/13 (5.4%)	0.088	107 (44.8%)/59 24.7%)
Etiology of craniectomy (%)		0.635		0.181	
Traumatic brain injury	8 (5.3%)		41 (27.0%)		103 (67.7%)
Hemorrhagic stroke	5 (10.0%)		11 (22.0%)		34 (68.0%)
Ischemic stroke	2 (11.8%)		1 (5.9%)		14 (82.3%)
Tumor	1 (7.1%)		1 (7.1%)		12 (85.8%)
Brain abscess	1 (16.7%)		2 (33.3%)		3 (50.0%)
Interval between craniectomy and cranioplasty, days, (IQR)	93 (56.5,422.25)	0.006	48.5 (27.75, 73.25)	0.391	47.5 (31.8, 87)
Lateralization of cranioplasty (%)		0.715		0.105	
Unilateral	16(7.4%)		47 (21.9%)		152 (70.7%)
Bilateral	1(4.2%)		9 (37.5%)		14 (58.3%)
The type of cranioplasty material (%)		< 0.001		0.505	
Autologous	11 (5.1%)		50 (23.4%)		153 (71.5%)
Artificial materials	6 (24.0%)		6 (24.0%)		13 (52.0%)
Post-craniectomy seizures (%)		0.001		0.270	
Early	1 (3.2%)		11 (35.5%)		19 (61.3%)
Late	5 (26.3%)	0.001$^{\Diamond}$	4 (21.1%)	0.766$^{\Diamond}$	10 (52.6%)
No seizure	11 (5.8%)		41 (21.7%)		137 (72.5%)
Prophylatic AEDs (%)		0.338		0.270	
No	2 (3.2%)		17 (27.0%)		44 (69.8%)
Yes	9 (7.1%)		24 (19.0%)		93 (73.8%)
Pre-cranioplasty hydrocephalus (%)		0.128		0.619	
No	12 (6.0%)		46 (23.1%)		141 (70.9%)
Yes	5 (12.5%)		10 (25.0%)		25 (62.5%)
Neurological deficits (%)$^{\#}$		0.825		0.042	
No	7 (7.3%)		16 (16.7%)		73 (76.0%)
Yes	10 (7.0%)		40 (28.0%)		93 (65.0%)
> 2 unprovoked seizures	4(10.3%)		35(89.7%)		0

Abbreviations: AEDs, antiepileptic drugs; n, number of cases; IQR, inter-quartile range; $^{\Delta}$ compared with no post-cranioplasty seizures; $^{\Diamond}$compared with no post-craniectomy seizures; $^{\#}$ neurological deficits including cognitive impairment, aphasia, or focal motor deficits; *one of the patients had early and late seizures.

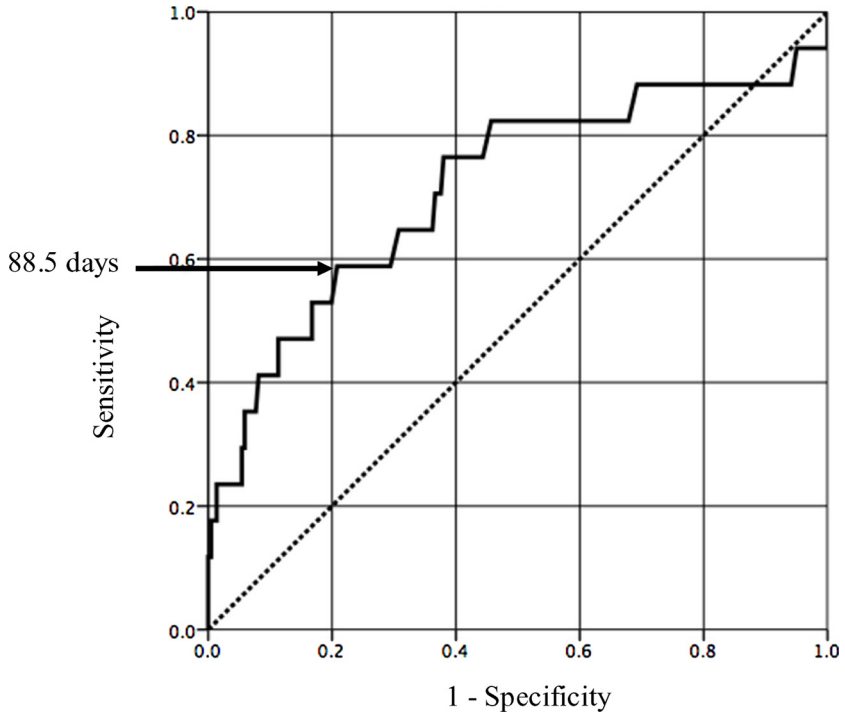

Fig. 2. ROC curve for post-cranioplasty early seizures and interval of craniectomy and cranioplasty (area under the curve 0.717; 95% CI 0.565–0.868; P = 0.003). The size maximizing the addition of sensitivity and specificity was 88.5 days (sensitivity 58.8%, specificity 77.8%).

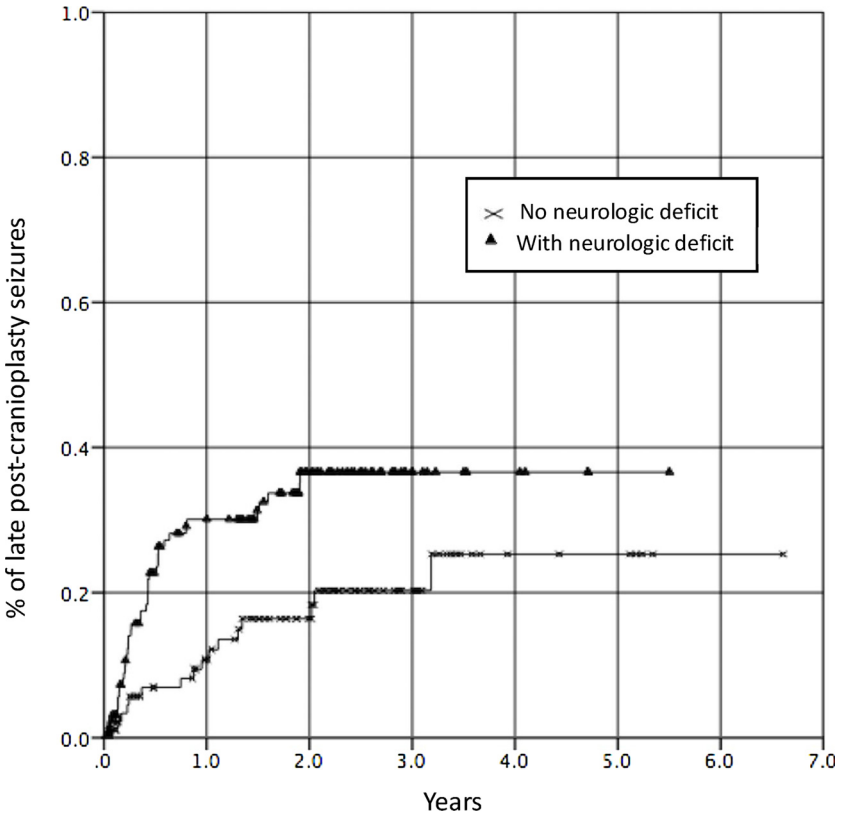

Fig. 3. Kaplan-Meier curve for percentage of late post-cranioplasty seizures and comparing between with/without neurologic deficit (Log-rank P = 0.009).

seizures. This may be due to that cranioplasty still can change the intracranial and cerebral prefusion pressures, which provoke early seizures as previously discussed [4,28,29].

We further identified that use of artificial materials was a risk factor for early post-cranioplasty seizures in both groups (with and without seizures before cranioplasty), which has not been reported in previous studies [8,27]. Artificial material might be less fit to the skull deficit resulting in enlargement of the intracranial volume or compression of the brain tissue [13,27,30]. In addition, hydrocephalus was a risk factor for early post-cranioplasty seizures only in the subgroup of patients who

Table 3
Risk factors for post-cranioplasty seizures in patients without post-craniectomy seizures.

	Early post-cranioplasty seizures n = 11	*p* value$^{\Delta}$	Late post-cranioplasty seizures n = 41*	*p* value$^{\Delta}$	No post-cranioplasty seizures n = 137
Median age (years, IQR)	51 (42, 70)	0.756	52 (39.75, 63.75)	0.806	55 (36, 65.5)
Male/Female (%)	7 (3.7%)/4 (2.1%)	0.890	29 (15.3%)/12 (6.3%)	0.548	90 (47.6%)/47 (24.9%)
Etiology of craniectomy (%)		0.548		0.446	
Traumatic brain injury	4 (3.5%)		28 (24.8%)		81 (71.7%)
Hemorrhagic stroke	4 (9.1%)		10 (22.7%)		30 (68.2%)
Ischemic stroke	2 (13.3%)		1 (6.7%)		12 (80%)
Tumor	1 (7.7%)		1 (7.7%)		11 (84.6%)
Brain abscess	0 (0%)		1 (25%)		3 (75%)
Interval between craniectomy and Cranioplasty (days, IQR)	96 (64,223)	0.010	48.5 (27.75, 73.25)	0.645	47.0 (31.5, 84.5)
Lateralization of cranioplasty (%)		0.749		0.013	
Unilateral	10(5.8%)		33 (19.3%)		128 (74.9%)
Bilateral	1(5.6%)		8 (44.4%)		9 (50%)
The type of cranioplasty material (%)		0.024		0.588	
Autologous	8 (4.6%)		39 (22.4%)		127 (73.0%)
Artificial materials	3 (20%)		2 (13.3%)		10 (66.7%)
Prophylatic AEDs (%)		0.337		0.269	
No	2 (3.2%)		17 (27.0%)		44 (69.8%)
Yes	9 (7.2%)		24 (19.0%)		93 (73.8%)
Pre-cranioplasty hydrocephalus (%)		0.699		0.168	
No	10 (6.2%)		32 (19.9%)		119 (73.9%)
Yes	1 (3.6%)		9 (32.1%)		18 (64.3%)
Neurological deficits (%)$^{\#}$		0.899		0.075	
No	5 (6%)		13 (15.7%)		65 (78.3%)
Yes	6 (5.7%)		28 (26.4%)		72 (67.9%)

Abbreviations: AEDs, antiepileptic drugs; n, number of cases; IQR, inter-quartile range; $^{\Delta}$ compared with no post-cranioplasty seizures; $^{\Diamond}$compared with no post-craniectomy seizures; $^{\#}$ neurological deficits including cognitive impairment, aphasia, or focal motor deficits; *one of the patients had early and late seizures.

Table 4
Risk factors for post-cranioplasty seizures in patients with post-craniectomy seizures.

	Early post-cranioplasty seizures n = 6	*p* value$^{\Delta}$	Late post-cranioplasty seizures n = 15	*p* value$^{\Delta}$	No post-cranioplasty seizures n = 29
Median age (years, IQR)	64 (54.75, 83.5)	0.218	57 (38, 56)	0.287	59 (36, 72)
Male/Female (%)	4 (8%)/2 (4%)	0.714	14 (28%)/1 (2%)	0.017	17 (34%)/12 (24%)
Etiology of craniectomy (%)		0.236		0.396	
Traumatic brain injury	4 (10.3%)		13 (33.3%)		22 (56.4%)
Hemorrhagic stroke	1 (16.7%)		1 (16.7%)		4 (66.7%)
Ischemic stroke	0 (0%)		0 (0%)		2 (100%)
Tumor	1 (50%)		0 (0%)		1 (50%)
Brain abscess	0 (0%)		1 (100%)		0 (0%)
Interval between craniectomy and cranioplasty, days, (IQR)	158.5 (30.75,719.5)	0.272	44 (23, 75)	0.414	48 (33, 126.5)
Lateralization of cranioplasty (%)		0.272		0.333	
Unilateral	6(13.7%)		14 (31.8%)		24 (54.5%)
Bilateral	0 (0%)		1 (16.7%)		5 (83.3%)
The type of cranioplasty material (%)		0.019		0.161	
Autologous	3 (7.5%)		11 (27.5%)		26 (65%)
Artificial materials	3 (30%)		4 (40%)		3 (30%)
Post-craniectomy seizures (%)		0.028		0.598	
Early	1 (3.2%)		11 (35.5%)		19 (61.3%)
Late	5 (26.3%)		4 (21.1%)		10 (52.6%)
Pre-cranioplasty hydrocephalus (%)		0.041		0.154	
No	2 (5.3%)		14 (36.8%)		22 (57.9%)
Yes	4 (33.3%)		1 (8.4%)		7 (58.3%)
Neurological deficits (%)$^{\#}$		0.777		0.582	
No	2 (15.4%)		3 (23.1%)		8 (61.5%)
Yes	4 (10.8%)		12 (32.4%)		21 (56.8%)

Abbreviations: AEDs, antiepileptic drugs; n, number of cases; IQR, inter-quartile range; $^{\Delta}$ compared with no post-cranioplasty seizures; $^{\#}$ neurological deficits including cognitive impairment, aphasia, or focal motor deficits.

had pre-cranioplasty seizures, which can also be explained by the change of intracranial pressure.

In patients developed late onset seizures after cranioplasty, bilateral cranioplasty was a risk factor in the subgroup of no post-craniectomy seizures. Patients underwent bilateral craniectomy are likely to have more severe brain damage than unilateral craniectomy patients. Near two-third 16 (66.7%) patients undergoing bilateral craniectomy had neurologic deficits, which is in accordance to the observation that neurological deficits are associated with the development of late seizures (Fig. 3).

This study has several limitations. First, the study is retrospective. Second, post-cranioplasty seizures were defined by a clinician sometimes without electroencephalography data, and pseudoseizures could be a confounding factor. Lastly, the sample size is relatively small. Studies with larger cohorts are necessary to generate more powerful conclusions and to refine the predictors of post-cranioplasty seizures.

5. Conclusions

Post-operative seizures were the most common complication after cranioplasty. The occurrence of early and late seizures was associated with different risk factors. The temporary physiological stress of surgery on the pre-existing propensity to develop seizures is probably responsible for early seizures, while late seizures represent a reduced seizure threshold of neuronal damage. Further studies are necessary to elucidate whether earlier cranioplasty can reduce the incidence of post-cranioplasty seizures.

Disclosure of funding sources and conflict of interest

None of the authors have any commercial associations, such as consultancies, stock ownership, or other equity interests or patent-licensing arrangements that may influence this study.

Authors' contributions

FY Shih participated in the design of the study and drafted the manuscript. HC Wang, JT Ho, and WF Chen participated in sequence alignment and clinical evaluation of the patients. FY Shih and HC Wang performed the statistical analysis. MH Tsai and WF Chen conceived the study, participated in its design and coordination, and helped draft the manuscript. All authors read and approved the final manuscript.

Ethical approval

The study was approved by Chang Gung Memorial Hospital's Institutional Review Committee on Human Research.

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