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The Current Analysis of the Risk Factors for Bone Graft Infection after Cranioplasty

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Objective: The aim of this study is to investigate the factors that may be related to bone graft infection and to contribute to lower the infection rate. According to current studies, the rate of bone graft infection after cranioplasty was reported up to 15.9% and this is significantly high. There are many analyses of the factors influencing bone graft infection, but this issue may need to be reconsidered in that the current medical environment is ever-changing.
Methods: We retrospectively reviewed the demographic, clinical data of 130 patients who underwent cranioplasty following decompressive craniectomy from January 2004 to December 2011. We analyzed several factors influencing bone graft infection and divided them into three categories of clinical, operation-related and hematological factors including white blood cell count, erythrocyte sedimentation rate, C-reactive protein and albumin. Statistical significance was done by chi-square test, Fisher's test and Mann-Whitney U test.
Results: The infection occurred in 12 patients in 130 cranioplasties (9.2%). There was no difference in infection rate between each group of early and later surgery, graft material, cause of craniectomy. Among many factors, low Glasgow Coma Scale (GCS≤8) and combined ventriculoperitoneal (VP) shunt were significantly correlated with bone graft infection (p=0.025, p=0.025, respectively). There was no statistically significant difference in hematological analysis between groups.
Conclusion: Low GCS and combined VP shunt with cranioplasty may increase the risk of bone graft infection.
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KEY WORDS: Cranioplasty · Craniectomy · Infection · Risk factor.

Introduction

Cranioplasty is a surgical procedure that repairs irregularity or imperfection of skull after craniectomy for several causes such as traumatic or vascular insults. This is done to restore cerebral protection, improve cosmesis, normalize intracranial pressure, and provide an intact skull vault. After cranioplasty, delayed infection and bone resorption are two common complications and the estimated incidence of bone graft infection is ranging from 1% to 15.9% depending on the presence of certain risk factors.[14] Infection may be associated with increased morbidity because of the need for removal of the flap, a course of long-term intravenous antibiotics, and replacement at a later time.[4,18] Therefore, prevention for infection is thought to be most important.

The risk factors of the cranioplasty infection may differ according to the authors and patients populations and there are many previous analyses of the factors influencing bone graft infection. But we need to pay attention to this matter as the current medical environment is ever-changing and the influencing risk factors are also expected to be changed. Therefore, we analyzed the cranioplasties done in recent 8 years and tried to identify the correlation between the infection and the predictive factors.

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Materials and Methods

We retrospectively reviewed the records of 140 patients who underwent a cranioplasty following decompressive craniectomy from January 2004 to December 2011. Among 140 patients, we excluded 10 patients due to loss of follow-up and

short-term postoperative follow-up less than 3 months. Cranioplasty was performed by several different neurosurgeons, but all the bone flaps removed during the craniectomy were frozen and stored in bone bank at below −80℃ and they were soaked in betadine solution and irrigated with normal saline before use. The selection of bone graft material was basically autogenous bone except when autogenous bone flap was lost or broken into small pieces. In most cases of artificial cranioplasty, polymethyl methacrylate (PMMA) and hydroxyapatite bone cement with titanium plate or CranioFix® (Aesculap AG, Tuttlingen, Germany) were used to remodel the defected skull and to fix the flap.

Generally, postoperative wound infection include purulent wound discharge, bacterial meningitis, epidural and subdural empyema, osteomyelitis, wound cellulitis and so on. In this study, however, we defined bone graft infection as only for the cases which required the removal of the infected bone graft. The mere local signs such as skin redness, tenderness and pus-like discharge controlled by antibiotics only were not regarded as bone graft infection.

We divided the possible risk factors into 3 categories of clinical, operation-related and hematological factors and studied the correlation between the infection and the predictive factors. The following factors such as sex, age, medical cormobidities such as hypertension (HTN) and diabetes mellitus (DM), cause of craniectomy, Glasgow Coma Scale (GCS), timing of cranioplasty were taken into consideration. Also, we analyzed the number of previous operations, mean operation time, graft material, combined ventriculoperitoneal (VP) shunt to investigate the correlation with infection rate. We also performed hematological analysis including white blood cell (WBC) count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) as the inflammatory markers and albumin which rather reflects inflammatory conditions.

Patient characteristics

In this study, we reviewed 130 patients containing 91 male and 39 female, with the mean age of 54.0 years. The follow-up period ranged from 3 months to 7.3 years and the mean follow-up period was 24.7 months. The initial diagnosis was grouped into trauma vs. non-trauma group and there were 62 and 68 patients respectively. Skull defects were consequent to: head injuries (62 cases), vascular disease including spontaneous subarachonoid hemorrhage (39 cases) and cerebral infarction (15 cases), hypertensive intracranial hemorrhage (7 cases), brain tumor (7 cases). The average time interval between craniectomy and cranioplasty was 3.2 months. Among 130 patients, autogenous bone graft was used in 107 (82.3%) patients, whereas allogenous bone graft was used in 23 (17.7%) patients. The mean operation time was 154.5 minutes for autogenous bone graft and 216.5 minutes for allogenous bone graft. GCS before cranioplasty was divided into two subgroups: GCS>8 and GCS≤8. 109 patients (83.8%) belonged to GCS>8 group and 21 patients (16.2%) belonged to GCS≤8 group. In the current study, 97 (74.6%) patients underwent one operation and 33 patients (25.4%) underwent two or more operations between craniectomy and cranioplasty. As for combined operation, 21 patients (16.2%) simultaneously had VP shunt with cranioplasty (Table 1).

TABLE 1. Patient demographics

Variables	Number of patients (%)
Number of patients	130
Male	91 (70.0)
Female	39 (30.0)
Age (years±SD)	54.0±17.4
Male	56.1±21.7
Female	53.7±15.1
Mean follow-up period (months±SD)	24.7±18.5
Initial diagnosis	
Trauma	62 (47.7)
Non-trauma	68 (52.3)
Vascular	54 (79.4)
Subarachnoid hemorrhage	39 (57.4)
Cerebral infarction	15 (22.0)
Hypertensive ICH	7 (10.3)
Brain tumor	7 (10.3)
Time interval between craniectomy and cranioplasty (months±SD)	3.22±1.6
Graft material	
Autogenous	107 (82.3)
Allogenous	23 (17.7)
Operation time (minutes±SD)	162.4±107.9
Autogenous	154.5±80.5
Allogenous	216.5±127.4
GCS before cranioplasty	
>8	109 (83.8)
≤8	21 (16.2)
Number of previous operation	
1	97 (74.6)
2	22 (16.9)
3	8 (6.2)
4	3 (2.3)
Combined VP shunt	
Yes	21 (16.2)
No	109 (83.8)

SD: standard deviation, GCS: Glasgow Coma Scale, VP: ventriculoperitoneal, ICH: intracerebral hematoma

Statistical analysis

SPSS 17.0 software (SPSS Inc., Chicago, IL) evaluated factors related to bone graft infection. Statistical significance was tested using chi-sqaure test, Fisher's test and Mann-Whitney U test. The results $p<0.05$ was considered statistically significant.

Results

We divided 130 patients into two groups; the infection group and the non-infected group. 12 infections were documented and the overall infection rate was 9.2%.

Clinical factors

Age and sex

The mean age of the infection group was 48.0 years, whereas that of the non-infected group was 54.6 years. There was no statistically significant difference between each group (p=0.097). The rate of bone graft infection in males was 9.89%, whereas that in females was 7.69%. There was no statistically significant difference between each group (p=1.000) (Table 2).

Medical comorbidities

The study included 37 (28.5%) cases of HTN and 24 (18.5%) cases of DM. But there was no statistically significant association in comorbidities and infection status (p=0.507, p=0.695, respectively)(Table 2).

Cause of craniectomy

The background diseases of the 130 cases were classified into two main categories: 62 (47.7%) cases with head trauma group and 68 (52.3%) cases with non-trauma group. Five cases (8.06%) with head trauma had bone graft infection, and seven cases (10.29%) without trauma had bone graft infection. For both groups, there was no statistically significant difference in the bone graft infection rate between groups of cause of craniectomy (p=0.767)(Table 2).

Glasgow Coma Scale

The number of each group divided into two subgroups of GCS>8 and GCS≤8 was 109 (83.8%) and 21 (16.2%), respectively. The infection rate in high GCS group was 6.42% and 23.81% in low GCS group which is much higher. Statistically, there was significant association between low GCS and higher infection rate (p=0.025)(Table 2).

Time interval between craniectomy and cranioplasty

The mean time interval after removal of bone flap of the infection group and the non-infected group were 2.0 and 3.5 months, respectively. We divided each group into two subgroups based on time interval of 2 month and the infection rate of early cranioplasty group was 8.06% and that of delayed cranioplasty group was 10.29%. But, there was no statistically significant association between time interval

TABLE 2. Clinical factors for bone graft infection after cranioplasty

Variables	Infection (+) n=12	Infection (−) n=118	Total (%) n=130	*p*-value
Mean age, years	48.0	54.6	54.0	0.097
Sex				1.000
Male	9 (6.9%)	82 (63.1%)	91 (70.0%)	
Female	3 (2.3%)	36 (27.7%)	39 (30.0%)	
Medical Cormobidities				
HTN	2 (1.5%)	35 (26.9%)	37 (28.5%)	0.507
DM	1 (0.8%)	23 (17.7%)	24 (18.5%)	0.695
Cause of craniectomy				0.767
Trauma	5 (3.8%)	57 (43.8%)	62 (47.7%)	
Non-trauma	7 (5.4%)	61 (46.9%)	68 (52.3%)	
GCS before cranioplasty				0.025
>8	7 (5.4%)	102 (78.5%)	109 (83.8%)	
≤8	5 (3.8%)	16 (12.3%)	21 (16.2%)	
Time interval, months				0.562
<2 months	5 (3.8%)	57 (43.8%)	62 (47.7%)	
≥2 months	7 (5.4%)	61 (46.9%)	68 (52.3%)	

HTN: hypertension, DM: diabetes mellitus, GCS: Glasgow Coma Scale

TABLE 3. Operation related factors for bone graft infection after cranioplsty

Variables	Infection (+) n=12	Infection (−) n=118	Total n=130	*p*-value
No. prev. operation				0.331
1 time	7 (5.4%)	85 (65.4%)	92 (70.8%)	
more than 2 times	5 (3.8%)	33 (25.4%)	38 (29.2%)	
Mean operation time, minutes±SD	200.8±134.9	158.5±89.1	162.4±125.6	0.553
Graft material				0.692
Autogenous	11 (8.5%)	96 (73.8%)	107 (82.3%)	
Allogenous	1 (0.8%)	22 (16.9%)	23 (17.7%)	
Combined VP shunt				0.025
Yes	5 (3.8%)	16 (12.3%)	21 (16.2%)	
No	7 (5.4%)	102 (78.5%)	109 (83.8%)	

SD: standard deviation, VP: ventriculoperitoneal

TABLE 4. Hematological factors for bone graft infection after cranioplasty

Variables	Infection (+) n=12	Infection (−) n=118	*p*-value
WBC±SD ($\times 10^9$ cells/L)	9.15± 3.28	7.51± 2.97	0.078
ESR±SD (mm/hr)	24.83±24.36	29.87±33.11	0.360
CRP±SD (mg/dL)	0.38± 0.45	1.14± 5.29	0.894
Albumin±SD (g/dL)	4.00± 0.68	3.79± 0.54	0.353

SD: standard deviation, WBC: white blood cell, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein

and infection rate (p=0.562)(Table 2).

Operation-related factors

Number of previous operation

We divided the patients into two groups by the number of previous operation. The patients who had one previous operation before cranioplasty were 92 (70.8%) and those who had more than two were 38 (29.2%). The infection rate of the group who had more than two times was higher (13.15%) than that one operation group (7.60%). But there was no statistically significant difference between groups (p=0.331) (Table 3).

Operation time

The mean operation time for the infection group was 200.8 ±134.9 minutes, whereas that of the non-infected group was 158.5±89.1 minutes. There was no statistically significant difference between each group (p=0.553)(Table 3).

Graft material

Of all 130 patients, 107 (82.3%) cases were applied autogenous bone graft and 23 (17.7%) cases were applied allogenous bone graft. The infection rate was 10.28% in group using autogenous material and 4.35% in allogenous group. But, there was no statistically significant association between graft material and infection status (p=0.692)(Table 3).

Combined operation

In the current study, 21 patients (16.2%) had VP shunt with cranioplasty simultaneously. The infection rate in combined VP shunt group was 23.81% and 6.42% in other group. There was statistically significant association between combined VP shunt and infection rate (p=0.025)(Table 3).

Hematological factors

We compared preoperative WBC, ESR, CRP and albumin of the infection group with those of the non-infected group. We checked the level of WBC, ESR, CRP and albumin which was done at least two weeks before cranioplasty. There was no significant difference in average WBC count, ESR, CRP and albumin levels between the two groups (p>0.05, respectively)(Table 4).

Discussion

Historically, there are evidences of cranioplasty having been performed in several early cultures, including pre-Columbian Incans using gold or silver plates, and the Celts using bone 'rondelles', and the first reported cranioplasty was probably that of a Russian who, after receiving a sword blow to the head, had the defect restored with a piece of dog's cranium in 1668.[16]

Bone graft infection is one of the main complications after cranioplasty and it is important to prevent before the oc-

currence, because it may result in substantial morbidity and usually requires removal of the infected bone. Generally, infection is the interaction of the host, microorganism and the environment. Previous infection due to penetrating open head injury appears to be possible risk factor. Also, introduction of foreign body like methyl methacrylate during the drilling of bone could be the risk factors for delayed infection.[14] Bacteria attached to the surface of a foreign body can remain alive and cause recurrent infection. Bacteria newly introduced from the environment may cause a first infection as well. Because scar tissue is less resistant to infection, secondary infection more likely arises from bacteria that have been dominant within the wound for a long period.[8,15] The risk factors for bone graft infection have been identified in many previous studies but it is still disputable.

As regards preservation of bone flap, all cases were freeze-preserved at below −80℃. According to recent study, cranioplasty using deep-freezing bone flap showed a low infection rate (2.3%), and cranioplasty using a bone flap banked in the patient's abdominal wall revealed no case of complications.[10] If the deep-freezer is not available, subcutaneous abdominal preservetion can be used for the bank of bone flap.[10]

Graft material

In the many previous studies, graft material is one of the main concerns of bone graft infection. In general, autogenous bone flap is the preferred one because of a theoretical decreased risk of immune rejection and its efficacy as a substrate for bony regrowth and revascularization.[2,18] According to Kim et al.[9] they analyzed 111 patients and the overall infection rate was 9.9%. In cases with frozen autogenous bone and allogenous bone material, the infection rate was 8.5% and 13.7% respectively, but there was no statistically significant difference between the two groups.

To be suitable for cranioplasty, the material must be biologically inert, nonresorbable, nonantigenic, relatively inexpensive, radiolucent, sterilizable and light-weight but strong enough to withstand impact.[6] In addition, the material should have low thermal and electrical conductivity and a low propensity for late infection. PMMA is one of the most commonly used allogenous material for cranioplasty. There is a controversy about relatively higher infection rate of autogenous vs. allogenous bone grafts. According to Yadla et al.[18] the current analysis containing eighteen articles showed no significant difference in infection rates between autogenous and allogenous grafts. In the present study, the infection rate of autogenous and allogenous bone grafts was 10.28% and 4.35% respectively, but there was no significant difference in rate between the two groups.

Timing of surgery

The second most common concern is timing of surgery and it may be the most disputable topic above all. It is common belief that the shorter time from craniectomy to cranioplasty is associated with poor outcome, and some investigators have reported the benefits of delayed cranioplasty.[7] Datti et al.[5] followed up 100 patients underwent cranioplasty and reported that the highest infection rate was seen in the 0−6 months group. Yamaura et al.[19] noted that all of their infected patients had undergone cranioplasty within 3 months of external decompression. Matsuno et al.[13] investigated 206 cases of cranioplasty and the time intervals after removal of bone flap of the infected group and the non-infected group. There was a statistically significant difference between the two groups and the mean time intervals of the infected group were shorter than that of the non-infected group. On the contrary, according to Archavlis and Nievas,[1] they divided 242 patients into three groups depending on the timing of cranioplasty; ultra early group of until 6 weeks, early group of 7 to 12 weeks and delayed group of after 13 weeks following craniectomy. They found that ultra early cranioplasty was a safe and successful strategy. But this is also a matter of controversy, and there are many studies showing timing of surgery has no effect on the rate of cranioplasty infections. According to Park et al.,[14] the infection rate was the highest when the operation was performed between 6 to 12 months, but this difference was statistically not significant. Lee et al.[11] also showed that the interval between craniectomy and cranioplasty did not significantly alter the infection rate. In the present study, mean time intervals after removal of bone flap of the infected group and non-infected group were 2.04 and 3.53 months, respectively. In addition, we tried to identify the time interval which is the most associated with the high infection rate. We divided each group into two subgroups based on time interval as 1, 2, 3 and 6 months. In all analysis, no statistically significant differences were observed between each group. This conclusion is limited and requires further analysis in a prospective study.

Glasgow Coma Scale

Next, we focused on GCS before cranioplasty as a predisposing risk factor for cranioplasty infection. In a recent study,[4] there was statistically significant association between low GCS (≤8) groups and higher infection rate. But there is no sufficient analysis on relationship between GCS before cranioplasty and the infection rate. In the present study, the

infection rate of subgroups are 6.42% (GCS>8) and 23.81% (GCS≤8), respectively and there was significant association between low GCS groups and higher infection rate. According to the report about impairment of non-specific immunity in patients under persistent vegetative state (PVS) resulting from trauma, we can consider the deficiency of immunity for the possible cause.[3] The level of human leukocyte antigen-DR expression on the surface of peripheral blood monocytes in PVS patients decreases obviously, and the function of non-specific immunity in PVS patients is suppressed.[3] It needs to pay more attention to the case of serious brain injury for prevention of infection before cranioplasty.

Emplacement of ventriculoperitoneal shunt during cranioplasty

In our study, emplacement of VP shunt during cranioplasty was associated with higher rate of infection. The infection rate in combined VP shunt group was 23.81% and it is significantly high than 6.42% of cranioplasty alone. The possible mechanism may be that cerebrospinal fluid shunting is thought to provide an opportunity for bacterial growth. Introduction of a foreign body is also a risk factor for infection because the bacteria attached to the surface of a foreign body can remain alive and cause recurrent infections.[8,17]

According to the previous study about operative modality and bone graft infection, Matsuno et al.[13] divided all the cranioplasties into three groups; delayed cranioplsty alone (154 cases), delayed cranioplasty with VP shunt (47 cases) and delayed cranioplasty with other operations such as clipping (5 cases). The rates of infection were 14.3%, 4.2% and 0%, respectively but there was no statistically significant difference among these groups. Post-traumatic hydrocephalus is a frequent complication secondary to severe traumatic brain injury and the incidence rate ranges from 0.7 to 51.4% in patients and surgical decompression itself can increase the incidence of hydrocephalus.[12] When the hydrocephalus is accompanied to the skull defect, VP shunt often needs to be performed with cranioplasty. But there are not enough study about the association between one-stage operation of VP shunt and cranioplasty and infection. So further study may be required and if the association is confirmed, we also need to investigate about the optimal time of VP shunt.

Hematological analysis

As regard to hematological findings in the present study, we checked the level of WBC, ESR, CRP and albumin at least two weeks before cranioplasty and performed cranioplasty only when the patient didn't show the sign of infection nor the elevated WBC, ESR, CRP. As a result, it is thought that this factor somewhat affected the result, and there were no statistically significant difference in hematological analysis between the infection group and non-infected group. Also, as for the albumin, it doesn't reflect the infectious status directly, but it reflects inflammatory condition including infection, trauma and surgery. Therefore we included albumin in the hematological analysis, but there was no significant difference between the groups.

Limitation

As the limitation of this study, the number of the infection group is small, so our data are limited to make definitive conclusions as to this point. Second, as for the graft material, the infection rate of autogenous material group was 10.28% and it is higher than 4.35% of allogenous group. But there was no statistically significant association between graft material and infection status. We couldn't describe the preservation of the bone flap in detail and the specific graft and fixation material due to the missing data as the review was conducted in a retrospective manner, and it may influence on the biased results. Third, in the present study, we defined bone graft infection as only for the cases which required the removal of the infected bone graft. If we included every suspected case of infection, the infection rate might be slightly high and it may be biased the results.

Conclusion

Based on our data, the low GCS and combined VP shunt operation with cranioplasty may increase the risk of bone graft infection.

■ The authors have no financial conflicts of interest.

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