

Outcome of the Subcutaneous Autologous Skull Flap Preservation in Traumatic Head Injury: Comparison between the Early and Late Cranioplasty

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บทคัดย่อ: ผลของการผ่าตัดเก็บรักษากะโหลกศีรษะผู้ป่วยใต้ผิวหนังในผู้ป่วยบาดเจ็บศีรษะ: เปรียบเทียบวิธีการผ่าตัดปิดกะโหลกทันทีเมื่อพร้อมและแบบรอระยะเวลา

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กลุ่มงานศัลยกรรม โรงพยาบาลปทุมธานี อำเภอเมือง จังหวัดปทุมธานี 12000

ภูมิหลัง: การผ่าตัดปิดกะโหลกศีรษะโดยใช้กะโหลกตัวผู้ป่วยเองมีความแข็งแรงได้รูปทรงสวยงามและลดปัญหาการถูกปฏิเสธเนื้อเยื่อของร่างกาย แต่ช่วงเวลาที่เหมาะสมของการผ่าตัดปิดกะโหลกศีรษะยังคงเป็นที่ข้อโต้แย้งกันอยู่ ระยะเวลา รอคอยการผ่าตัดปิดกะโหลกที่นานเกินไปมีผลต่อการฟื้นตัวของระบบประสาท **วิธีการ:** การศึกษาวิเคราะห์เปรียบเทียบย้อนหลัง ในผู้ป่วยบาดเจ็บศีรษะ 31 รายที่ได้รับการเก็บรักษากะโหลกใต้ผิวหนังและเปรียบเทียบผลการผ่าตัดปิดกะโหลกทันทีเมื่อพร้อม (early cranioplasty) และ การผ่าตัดแบบรอระยะเวลา (late cranioplasty) **ผล:** พบว่า การผ่าตัดกะโหลกศีรษะทั้ง 2 วิธี มีความปลอดภัย มีประสิทธิภาพและมีความเหมาะสมไม่แตกต่างกัน แต่การผ่าตัดแบบรอระยะเวลามีการสูญเสียมวลกระดูกของกะโหลกศีรษะส่งผลกระทบต่อรูปทรงศีรษะเนื่องจากการเปลี่ยนแปลงรูปร่างและขนาดของกะโหลกศีรษะ **สรุป:** การผ่าตัดปิดกะโหลกศีรษะควรทำเร็วที่สุดเมื่อผู้ป่วยเริ่มมีอาการฟื้นตัวดีแล้ว การผ่าตัดปิดกะโหลกทันทีเมื่อพร้อมเป็นวิธีที่มีความเหมาะสม

คำสำคัญ: ผู้ป่วยบาดเจ็บศีรษะ การเก็บรักษากะโหลกศีรษะใต้ผิวหนัง การผ่าตัดปิดกะโหลกทันทีเมื่อพร้อม การผ่าตัดปิดกะโหลกแบบรอระยะเวลา

Abstract

Background: The autologous skull flap cranioplasty has the potential strong bony fusion, replaced in the original position achieves the best cosmetic and eliminates the problem of rejection. The optimal timing for cranioplasty has remained controversial. The long waiting time for the cranioplasty affects the recovery of the neuronal function. **Method:** The retrospective comparative studied in thirty-one patients with traumatic head injury who underwent the subcutaneous autologous preservation and the outcome of the early and

late cranioplasty. **Results:** The early and late cranioplasty were safe, efficient, feasible technique and no differences between the two groups, but the late cranioplasty loss of bone mass and effect to reconstruction result in improper shape and size. **Conclusion:** Cranioplasty should be early performed when the patient is stable and the early cranioplasty is a suitable technique

Keywords: Traumatic head injury, Subcutaneous autologous skull flap preservation, Early cranioplasty, Late cranioplasty

Introduction

Craniectomy has gained more scientific evidence of therapeutic value in option for treatment of increased intracranial pressure resulting from brain edema with non-responding to medical treatment. The repair of skull defect is not only important for brain protection and early rehabilitation, to reconstruct the skull for cosmetic deformation but also improves neuronal function and the effects of motor trephine syndrome¹⁻⁴. In 1919, Kreider re-implanted skull defect from the skull flap that preserved between the abdominal fat and the muscle layers⁵ and Elliott and Scott used cryopreserved autogenous skull flaps in the blood bank before the frozen bone was replaced into the skull defect in 1948⁶. In 1975, Nakajima preserved skull flaps in the thigh and possible to get the fascia lata through the same skin incision for a large dural patch⁷. In 1986, Açıkgöz preserved rabbit skull flaps in the abdominal wall and revealed bony lacunae were filled with osteocytes in abdominal pocket and granulation tissue formation after cranioplasty with active osteoblasts, new blood vessels near the periosteum of the skull flap and bone regeneration⁸. In 1988 Korfali presented a technique for preserving the skull flap under the scalp after decompressive craniectomy until re-implantation when brain swelling had been resolved⁹.

The several autogenous skull flaps storage methods have been used such as alcohol storage, calcination, especially the subcutaneous abdominal wall and cryopreservation are more common that might be an effective and safe method for the storage as a result of survival of the bone cells and most commonly used to preserve autologous skull flaps but alcohol storage and calcination cause the bone cells to lose activity^{10, 11}. Although, many studies reported complications; the incidence infection rates were similar in the subcutaneous preservation and cryopreservation but the incidence of bone flap resorption in the cryopreservation was higher varied from 4% to 22% than the subcutaneous preservation^{12, 13}. Furthermore, contaminated bacteria could survive after long freezing and still have considerable growth capacity; skull flap resorption might cause active

osteoclasts was destroyed, bone cell death and foreign body reactions following cranioplasty^{13, 14}. In contrast, the subcutaneous storage method might keep the bone cells alive and better preservation method to maintain the biological characteristics of the bone flap^{8, 13, 15}.

Although synthetic materials have been developed to alternate skull flap, autologous skull flap has been widely used as the safe method and also provides the biological material that accepted completely at the graft site, increase bone regeneration, eliminates the problem of rejection, leads to very strong bony fusion, had the potential for assimilation, growth replaced in the original position achieves the best cosmetic and physiological results^{9, 16-18}. In our situation, preserving autologous skull flap after craniectomy in the subcutaneous abdominal wall for many patients if possible. According to several studies, the cranioplasty should be performed within 3 months to 12 months based on the presence of infections or postoperative complications¹⁹. Previously, accepted practice was for patients to wait for up to 6 months before having their skull reconstruction, but in some studied early surgery has no effect on the rate of cranioplasty infections and no significant increase in complication rates^{20, 21}. However, the optimal timing for preservation remains controversial. The aim of this study was to compare of the clinical outcomes and complications related between the early and late cranioplasty and the questions we wanted to address were the following:

1. Is the percutaneous cranioplasty feasible method for general hospital in Thailand?
2. Should we perform the early cranioplasty or late cranioplasty?
3. What are the precautions and complications for early and late cranioplasty?

Material and Method

A retrospective studied in 31 patients who underwent a reconstructive cranioplasty at the Department of Neurosurgery, Pathum Thani Hospital between October 2014 and Jan 2019. This study was defined as early cranioplasty when the time

interval between craniectomy and cranioplasty performed within 3 months and late cranioplasty when cranioplasty waited more than 3 months^{19,20,22}. The clinical data were collected from reviewing medical records included the patient age, gender, imaging studies, skull flap's weight, time interval between craniectomy and cranioplasty, perioperative finding and time since last follow-up. The sizes of the skull flap depended on patient's clinical, computer tomography and intraoperative finding which its effects on brain severity. The patients had Glasgow Coma Score less than 8, age more than 65 years and severe medical history were being excluded. The cranioplasty was performed as soon as possible when patients had clinical improvement (Glasgow outcome scale at least 4) and brain swelling was resolved.

This study was approved by the ethical review board of the Pathum Thani Hospital.

Surgical technique for skull flap preservation

After craniectomy was performed, the left paramedian abdominal incision was performed between the costal margin and the anterior superior iliac spine to prevent confusion if the patient undergoes other abdominal surgery. The dissection of a space under the subcutaneous tissue and muscular layer; then, placing of the skull flap in abdominal pocket²³. The fractured skulls were reconstructed prior to storage and the contaminated skull flaps were discarded. Before re-implantation, all patients underwent prophylactic antibiotic therapy and the skull flap was retrieved from the abdomen then washed with an antiseptic solution. Mini-plates fixed the skull flap to the craniectomy edge and closed wound with negative pressure drainage system (Figure 1).



Figure 1

The fractured skull was repaired before stored in an abdominal pocket (a, b, and c).

The skull healed before retrieved for cranioplasty was performed (e and f)

Statistical Analysis

Descriptive statistics were used to compare clinical outcomes between both groups. The Shapiro-Wilk test was using the test for normal distribution. The variables compared using independent and paired samples t-test for parametric statistics when data were normal distribution and Mann-Whitney U test for non-parametric statistics when data were non-normally distributed. A significance value (p-value) and 95% confidence interval was reported. All statistical analysis was performed using SPSS

Results

Thirty-one patients were included in this study. The most of patients were male gender (89.47% in early and 58.33% in late craniectomy) and were in working age range. The early cranioplasty group was mostly extradural with or without intradural lesion (68.42%) and the patients were performed cranioplasty for a period of 44 to 78 days (average 54.42 days). The late cranioplasty group was intradural lesion (66.67%) and the patients were performed cranioplasty for a period of 123 to 350 days (average 210.92 days). The cause of injury was mostly traffic accidents (80.64%) (table 1- 4).

Table 1 Demographics and surgical factors

	Early cranioplasty group*	Late cranioplasty group**
Gender male/female	17/2	7/5
Intracranial lesion		
- Extradural with or without Intradural		
EDH&SDH with cerebral contusion	1	2
EDH with SDH	5	2
EDH with Diffuse SAH	2	-
EDH	5	-
- Intradural lesion		
Diffuse SAH with cerebral contusion	3	3
Diffuse SAH with SDH	1	3
SDH	2	1
ICH	-	1
Cause of injury		
Traffic accident	16	9
Body assault	2	3
Fall	1	-

* n = 19, ** n = 12

Table 2 Characteristics data of patients in early cranioplasty group (n=19)

Gender / age	Cause of Injury	Craniectomy to cranioplasty time interval (days)	Skull mass after Craniectomy (grams)	Skull mass before Cranioplasty (grams)	Skull mass change (%)	Length of stay after cranioplasty (days)
Male/ 16 years	traffic accident	46	92	94	2.17	11
Male/ 19 years	body assault	53	113	110	-2.65	10
Male/ 23 years	traffic accident	57	84	85	1.19	11
Female/ 27years	traffic accident	49	76	74	-2.63	12
Male/ 27 years	body assault	48	102	105	2.94	10
Male/ 31 years	traffic accident	51	85	86	1.18	10
Female/ 35 years	traffic accident	44	81	83	2.47	11

Table 2 Characteristics data of patients in early cranioplasty group (n=19) (Cont.)

Gender / age	Cause of Injury	Craniectomy to cranioplasty time interval (days)	Skull mass after Craniectomy (grams)	Skull mass before Cranioplasty (grams)	Skull mass change (%)	Length of stay after cranioplasty (days)
Male/ 38 years	traffic accident	52	93	90	-3.23	11
Male/ 42 years	traffic accident	47	78	77	-1.28	10
Male/ 46 years	traffic accident	50	84	82	-2.38	10
Male/ 48 years	traffic accident	59	95	94	-1.05	11
Male/ 51 years	traffic accident	48	92	94	2.17	13
Male/ 58 years	fall	55	81	79	-2.47	12
Male/16 years	traffic accident	63	56	52	-7.14	13
Male/19 years	traffic accident	61	70	67	-4.29	13
Male/20 years	traffic accident	78	56	54	-3.57	9
Male/18 years	traffic accident	55	57	54	-5.26	19
Male/18 years	traffic accident	57	75	73	-2.67	16
Male/19 years	traffic accident	51	63	64	1.59	14

Table 3 Characteristics data of patients in late cranioplasty group (n=12)

Gender / age	Cause of Injury	Craniectomy to cranioplasty time interval (days)	Skull mass after Craniectomy (grams)	Skull mass before Cranioplasty (grams)	Skull mass change (%)	Length of stay after cranioplasty (days)
Female/ 22 years	traffic accident	183	86	79	-8.14	10
Male/ 19 years	body assault	210	77	60	-22.08	15
Female/ 20 years	traffic accident	350	90	74	-17.78	15
Male/ 39 years	traffic accident	226	86	75	-12.79	12
Male/ 22 years	body assault	306	42	30	-28.57	14
Male/ 60 years	traffic accident	161	80	65	-18.75	13
Male/ 45 years	traffic accident	220	47	38	-19.15	8
Female/ 46 years	traffic accident	251	57	45	-21.05	10
Female/ 63 years	traffic accident	174	72	60	-16.67	9
Male/ 30 years	traffic accident	153	69	60	-13.04	7
Male/ 17 years	traffic accident	174	51	45	-11.76	15
Female/ 38 years	body assault	123	75	72	-4.00	21

Numerical variables were normally-distributed, except age, craniectomy to cranioplasty time interval and length of stay after cranioplasty in the early cranioplasty group were non-normally distributed (table 4). The craniectomy to cranioplasty time interval in the late cranioplasty group was higher than the early cranioplasty group (median 52.00 vs 196.50 days, p-value <0.01). The age and length of stay after cranioplasty in the late cranioplasty group were higher than that in the early cranioplasty group, but the difference were not statistically significant (median 27.00 vs 38.50, p-value 0.18 and median 11.00 vs 12.50, p-value 0.80, respectively) (table 4 and 5). In early cranioplasty group, the skull flap mass

after craniectomy was average 80.68 grams (56 to 113 grams) and the skull flap mass before cranioplasty was average 79.71 grams (52 to 110 grams), but the difference was not statistically significant (p-value 0.07). In late cranioplasty group, the skull flap mass after craniectomy was average 69.33 grams (42 to 90 grams) and the skull flap mass before cranioplasty was average 58.58 grams (30 to 79 grams) (p-value <0.01) (table 4 and 6). Equal variances not assumed by Levene's test, the skull flap mass change in the late cranioplasty group was higher than the early cranioplasty group (mean -16.15% vs -1.31%, p-value <0.01) (table 4 and 7).

Table 4 Descriptive data and normality tests (Shapiro-Wilk normality tests)

	Mean±SD	Median (Min-Max)	p-value
Age (years)			
Early cranioplasty group*	30.05±13.43	27.00 (16-58)	0.02***
Late cranioplasty group**	38.09±17.88	38.50 (17-63)	0.08
Craniectomy to cranioplasty time interval (days)			
Early cranioplasty group*	54.42±8.36	52.00 (44-78)	0.04***
Late cranioplasty group**	210.92±65.63	196.50 (123-350)	0.35
Skull flap mass after craniectomy (gram)			
Early cranioplasty group*	80.68±15.67	81.00 (56-113)	0.63
Late cranioplasty group**	69.33±16.32	73.50 (42-90)	0.30
Skull flap mass before cranioplasty (gram)			
Early cranioplasty group*	79.71±16.57	82.00 (52-110)	0.70
Late cranioplasty group**	58.58±15.84	60.00 (30-79)	0.38
Skull flap mass change (%)			
Early cranioplasty group*	-1.31±2.91	-2.38% ((-7.14)-2.94)	0.22
Late cranioplasty group**	-16.15±6.63	-17.22% ((-28.57)-(-4.00))	0.99
Length of stay after cranioplasty (days)			
Early cranioplasty group*	11.90±2.42	11.00 (9-19)	0.01***
Late cranioplasty group**	12.42±3.92	12.50 (7-21)	0.48

* n=19, ** n=12, *** p<0.05

Table 5 The Mann-Whitney U Test to determine the median difference between age, craniectomy to cranioplasty time interval and length of stay after cranioplasty in early cranioplasty group and late cranioplasty group.

		p-value
Age (years old)	Early cranioplasty group*	0.18
	Late cranioplasty group**	
Craniectomy to cranioplasty time interval (days)	Early cranioplasty group*	<0.01***
	Late cranioplasty group**	
Length of stay after cranioplasty (days)	Early cranioplasty group*	0.80
	Late cranioplasty group**	

* n=19, ** n=12, *** p<0.05

Table 6 The Paired samples t-test to determine the mean difference between skull flap mass (grams) after craniectomy and before cranioplasty in the early cranioplasty group and late cranioplasty group

	Mean±SD	95%CI		p-value
		Lower	Upper	
Early cranioplasty group*	1.11±2.49	-0.10	2.31	0.07
Late cranioplasty group**	10.75±4.18	8.09	13.40	<0.01***

* n=19, ** n=12, *** p<0.05

Table 7 The independent samples t -test to determine the mean difference of the skull flap mass change (%) between early and late cranioplasty group

	Mean±SD	Mean Diff	95%CI		p-value
			Lower	Upper	
Early cranioplasty group*	-1.31±2.91	14.84	10.48	19.20	<0.01***
Late cranioplasty group**	-16.15±6.63				

* n=19, ** n=12, *** p<0.05

There were 8 in 31 cases (4 cases in early and 4 cases in late cranioplasty) had fracture which repaired before preserved in abdominal pocket and

7 in 8 cases have bone healing before retrieved for cranioplasty (3 in 4 cases in early cranioplasty group and 4 in 4 cases in late cranioplasty group) (Figure 2).

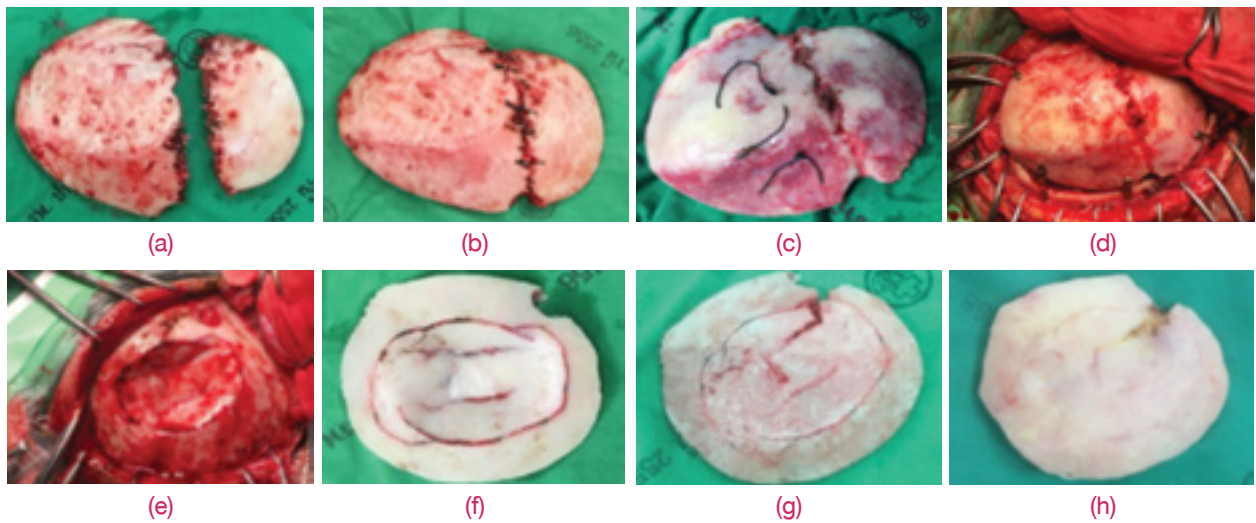


Figure 2

Diasteric skull fracture (a, b, c and d) and simple depressed skull fracture healed before retrieved for cranioplasty (e, f, g and h)

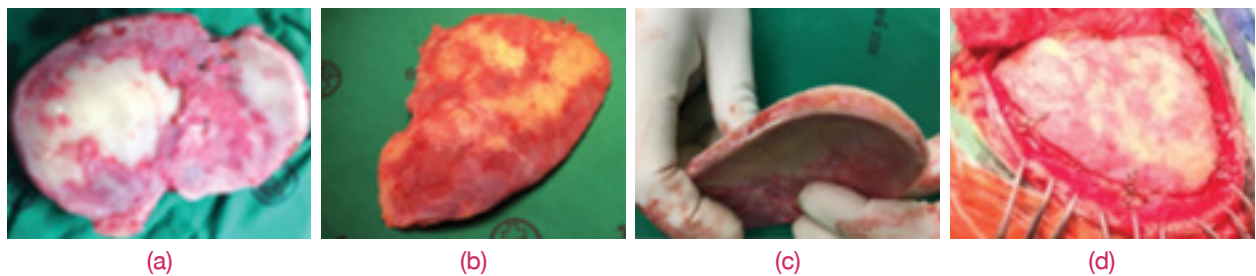


Figure 3

Red-whitish granulation tissue with a hard consistency (a) and neovascularization on the skull flap surface (b).

The contacted surface of the skull flap was prepared for cranioplasty (c) and a narrow gap between the skull flap and recipient site has been fixed (d).

The bone healing started to form at the edges of the skull flap during the 6 months after cranioplasty (Figure 4 (c)). Three of those cases developed a hydrocephalus after craniectomy (two cases in early and one case in late cranioplasty group) and had

a ventriculoperitoneal shunt placed at the time of cranioplasty. No patients had the skull flap re-implanted because of infection, cosmetic or serious complications.



Figure 4

Bone healing process show in CT scan at 1,3,6 and 12 months, respectively. (a, b, c and d).

Discussion

The indications for cranioplasty are protection of the vulnerable brain, cosmesis and facilitation of physiotherapy and mobilization²⁴. In patients with skull defects, the reconstruction cannot take place until the cerebral swelling has settled. Although 6 months are considered the minimum time to reduce complications from infection, cranioplasty performed within 3 months from craniectomy may lead to greater effects on motor functions^{10,19}. An early cranioplasty seems to reduce neurological complications, especially motor and cognitive recovery. Several studies have shown that patients who underwent early cranioplasty had better functional outcomes than late cranioplasty¹⁹.

1. Is the percutaneous cranioplasty feasible method for general hospital in Thailand?

In our situation, preserving autologous skull flap in abdominal wall pocket did not perform in the routine. The patients were selected from prognostic factor depends on the patient's condition which its effects on intracranial dynamics and to predict of survival outcome. Initial Glasgow Coma Score, pupil respond, vital sign, computed tomography, age, and intraoperative finding were used as a combined prognostic parameter²⁵. Although there is still no existing reports that have compared the subcutaneous preservation and cryopreservation in terms of the time duration of preservation related skull flap resorption, the incidence of skull flap resorption in the cryopreservation was higher than the subcutaneous preservation and more frequently in traumatic brain injury, multiple skull fractures and infection¹³. The skull flap resorption develops most frequently within the first year after cranioplasty

and wound healing disturbance or abscess within 2 months after cranioplasty²⁶. Therefore, the cryopreservation is unsuitable and limitations in a general hospital in Thailand because the blood bank does not have enough time to keep the skull flap. In our result of the study, preserving autologous skull flap under percutaneous tissue is the simplest technique, feasible and suitable than other methods in the general hospital, but it has to be appropriated preservation.

Although the alternative surgical techniques and other materials are developed to prevent the complications, various materials have been adapted to counter these pitfalls²⁷. The synthetic materials have a high complication rate, including implant failure and subacute or chronic infection²¹. Methyl methacrylate is a commonly used synthetic material because of its excellent tensile strength, strong, heat resistant and ease of use, but its fracture susceptibility, high risk of infection and the residual monomer from cold polymerization may be toxic have made this a less viable material long term²⁸. In Thailand, cranioplasty using synthetic materials are more expensive than cranioplasty using an autologous skull flap. Thus, cranioplasty using autologous skull flap is more economic than synthetic materials because it is the simplest, inexpensive and most suitable material that biocompatible without any risk of disease transmission^{24,29}.

2. Should we perform the early cranioplasty or late cranioplasty?

The study found after retrieving skull flaps from abdominal pocket reveal red-whitest granulation tissue and neovascularization on the skull flap surface

(Figure 3 (a) and (b)). Indeed, the fractured skull had bone healing process in abdominal pocket was observed in early and late cranioplasty show that placing the skull flap between subcutaneous tissue and the muscle layers can preserve and heal fracture skull. Tsukagoshi presented the neovascularized skull flap when preserved into the subcutaneous and onto the rectus abdominis muscle pocket¹⁷ and Wang found osteocytes and mature bone matrix embedded skull flap with attached periosteum subcutaneously in abdomen pocket³⁰. However, the storage skull flap in abdominal wall pocket for a long time causes the bone mass to lose. The cause of bone resorption is considered to occur in a solitary bone flap without bone fusion or in portions of the bone flap far away from the fusion site. The bone resorption in late cranioplasty is more than early cranioplasty, so that its size does not match the size of the skull window and affect to cosmetic result in improper shape and size³¹ (Figure 5).

The optimal time for skull flap replantation should be performed between the second and third months after craniotomy. Marked resorption can be avoided as long as the replantation time is less than 6 months³⁰. In our study showed the long time interval made skull flap mass and shape changes. In late cranioplasty group, it is difficult to fix the widening gap between the flap and the surrounding skull margin because significant loss of the skull flap mass resulted in its size is not matching the size of the skull window. The large area of the autologous skull flap with no periosteum attachment have an effect on the regrowth of bone grafts in the bone healing process. As granulation tissue proliferates, capillaries invade the reinserted bone flap from surrounding tissue and the periosteum infiltrate the reinserted bone, primitive progenitor cell migrates and bone remodeling occurs¹⁸. A lack of vascular supply often leads to nonunion and avascular necrosis³². The skull defected reconstruction should be early performed when the patient has improved condition.

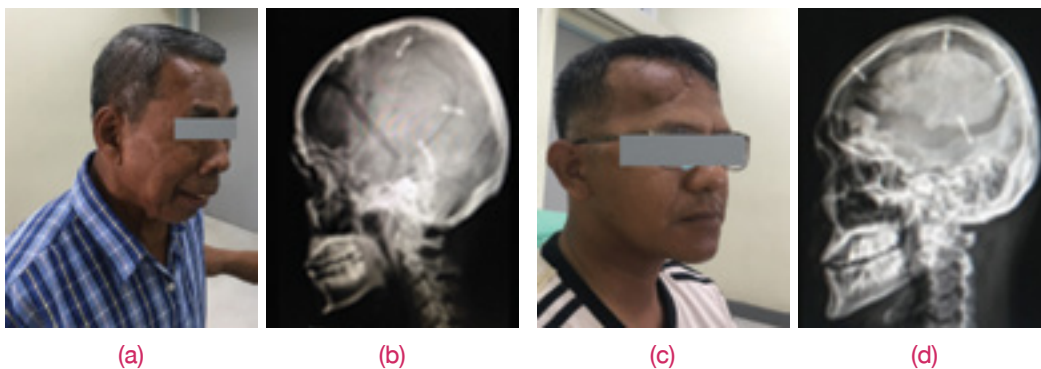


Figure 5

Show the patient's head was performed early cranioplasty is naturally symmetrical shape (a and b).

In late cranioplasty group, the loss of bone mass affects to reconstruction result from improper shape and size (c and d).

3. What are the precautions and complications for early and late cranioplasty?

Although the postoperative complication rate of 10% - 40% has been reported in large cranioplasty series. The severe complications of subcutaneous abdominal preservation in traumatic

head injury patients with traumatic brain injury required readmission by the hospital or reoperation about 30% of all complications, the high rate of failure of autologous skull flap cranioplasty from bone resorption and infection^{20, 21, 30}. However, the meta-analysis showed no difference in the time interval

between early and late cranioplasty in the overall complication and postoperative infection rate^{15,22}.

In our study, there were no differences complication in two groups such as reoperation or skull flap infections and others serious complication except in the late cranioplasty group and the large skull flap size complained discomfort symptom at an abdominal surgical site because had waited until patients' consciousness and the cerebral swelling was improved conditions before cranioplasty. However, the skull flap size could be difficult to fix because of the widening gap between the flap and skull margin in the late cranioplasty group. The incidence of bone resorption significantly correlated with an increased skull defect area, the skull flap size, extensive scarring that make it the most resistant to conditions like poor vascularity. The contacted surface of skull flap and window edge should be prepared for cranioplasty and narrow contact between skull flap and recipient site with rigid fixation has been discussed in the bone healing and bone fusion process, leading to ischemia bone is gradually reabsorbed (Figure 2 (c) and (d))³³⁻³⁵. Thus, reducing the skull flap size and shape result in bone healing and cosmesis when patients have performed late cranioplasty then should be early performed when the patient is stable.

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Conclusion

The subcutaneous autologous skull flap preservation is safe, efficient and feasible technique, suitable for institutions that do not have a blood bank. Furthermore, autologous skull flap cranioplasty is well accepted by patients for correction of the skull defect. In patients who have undergone craniectomy and have a good prognosis, should not have to wait cranioplasty for a long time, the early and late cranioplasty were no differences complication. However, in late cranioplasty loss of bone mass and effect to reconstruction result from improper shape and size. In Thailand, cranioplasty using autologous skull flap is more economic than synthetic materials and cryopreservation of skull flaps requires special equipment that cannot generally possible at general hospitals. The limitation of this study did not compare to cranioplasty using other materials or with autologous skull preserved in different modalities, and the long term follow-up, we could not estimate whether every skull flap resorption in computerized tomography scan because all the limitations of small sample size and retrospective analysis.

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