3 Cranioplasty: Does Timing Have Any Effect on the Degree of Neurological Recovery or the Complication Rate?

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Introduction

Decompressive craniectomy is commonly performed to relieve elevated intracranial pressure caused by trauma, stroke, hemorrhage, or edema [1–9]. Cranioplasty is often subsequently performed to restore cranial cosmesis, provide cerebral protection, and facilitate neurological rehabilitation [10, 11]. Cranioplasty itself has been shown to provide neurological improvement and the question of how long to wait before cranioplasty has received considerable attention [12–18]. Most surgeons wait for recovery from the initial indication for decompressive craniectomy with resolution of edema and inflammation, but often these patients can be lost to follow up for months to years [19]. Recent studies indicate that earlier cranioplasty may improve neurologic recovery and avoid certain complications [12, 15, 18, 19]. This chapter will use findings from two published meta-analyses on the association between the timing of cranioplasty on neurological improvement and complication rate to evaluate the current level of evidence and provide clinical and research recommendations [12, 18].

Method

For both studies, a systematic literature review was conducted in accordance to Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [20]. The search strategy was designed in accordance to Peer Review

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of Electronic Search Strategies (PRESS) criteria [21]. The search string was for the keywords "cranioplasty, early" or "cranioplasty, timing" in the title, abstract, or keyword list. The search was conducted in PubMed/MEDLINE, Scopus, and the Cochrane databases for original clinical studies published between January 1990 and April 2016. The references of literature reviews, meta-analyses, and included studies were also reviewed for further articles for inclusion. The quality of included individual articles were assessed using the Oxford Center for Evidence Based Medicine (OCEBM) guidelines [22]. The quality of evidence and resulting strength of recommendations were assessed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) guidelines [23].

Data Analysis

Complete details of the data analysis is reported in the relevant prior publications by this research group [12, 18]. Data were analyzed using Review Manager 5.3.5 (The Cochrane Collaboration, London, United Kingdom).

Neurological Outcome

For the neurological improvement outcome analysis, all but one study dichotomized patients into "early" and "late" cohorts based on time interval between craniectomy and cranioplasty most often using a threshold at or near 90 days. We followed this convention in our analysis: "early" cranioplasty was defined as less-than-or-equal-to 90 days after craniectomy, "late" was defined as beyond 90 days. For studies that did not provide raw data or used a different time-point than 90 days, the study's reported definition was accepted.

The standard mean difference (SMD) was used to normalize neurological measures to allow for comparison across different outcome scales. Change in pre- and postcranioplasty scores was compared between early and late groups to evaluate the difference in magnitude of neurological change over the follow-up period. The difference in means and standard deviation of the difference between sample means was used for this calculation.

The pre-cranioplasty neurological status of early and late cranioplasty groups was then compared to determine preoperative similarity between both groups. Finally, raw postcranioplasty neurological scores were compared to evaluate difference in final outcome. The reported mean and standard deviation from each study was used for these calculations.

Complications

For the complications analysis, complications were first grouped by specific type (e.g. overall complications, infection, seizure, etc.) and analysis was done comparing trauma and mixed populations. If overall complications were not reported in a

study, individual complications were summed. Complications were then grouped by "early" and "late" cranioplasty time-points. "Early" cranioplasty was defined as less than or equal to 90 days after craniectomy. The 90-day time-point was chosen for several reasons: (1) in the authors' experience, cranioplasty procedures often occur around 90 days after initial craniectomy; (2) several studies utilized the median time to cranioplasty in their data as a cutoff for defining early/late time-points, which was around 90 days; (3) grouping around 90 days allowed for inclusion of more studies in the pooled analysis. Studies that provided raw timing data were dichotomized at this time-point for analysis. For studies that did not provide raw data or used a different time-point than 90 days, the study's reported definition was accepted, and the results were pooled in the overall analyses.

Results

The search, screening, and selection of articles for inclusion for both neurological outcomes and complications analyses are presented in the PRISMA flow diagram (Fig. 3.1). A total of 313 and 323 non-duplicate studies were screened from a search on comparisons between early and late cranioplasty in our previous analyses on neurological outcomes and the complications, respectively. No studies were identified for inclusion that were published prior to 2000. Detailed reasons for article exclusion is reported in our previous studies.

For the neurological outcomes analysis (Fig. 3.1a), 24 articles were identified from bibliographic review and 16 articles were excluded after full-text review. Five authors were able to provide data not included in the original publication that allowed inclusion in this analysis [24–27]. Eight studies were included in the neurological outcomes analysis.

The final eight included studies for the neurological outcomes analysis represent 551 cranioplasty procedures (248 early, 303 late). Table 3.1 lists individual study characteristics. All studies were either retrospective cohort studies or case series and met criteria for OCEBM Level 4 evidence. Indications for initial craniectomy included trauma (78% of patients), ischemic stroke (9.4%), subarachnoid hemorrhage (4.9%), unspecified intracerebral hemorrhage (4.7%), and infection (1.5%) among other less common indications. Four studies included only trauma patients [26, 28, 29, 31]. One study dichotomized early and late cranioplasty at 42 days and did not report data to allow regrouping around 90 days [28]. All other studies were dichotomized within 1 week of the 90-day threshold.

For the complications analyses (Fig. 3.1b), 58 articles were identified from bibliographic review and 33 articles were excluded after full-text review. Two articles were not in English but were included because they appeared in a previous meta-analysis on cranioplasty [15, 32, 33]. Twenty-five studies were included in the complications analysis.

The final twenty-five studies that met inclusion criteria for the complications analysis represented 3126 cranioplasty procedures (1421 early, 1705 late). Table 3.2 lists individual study characteristics. All were retrospective cohort

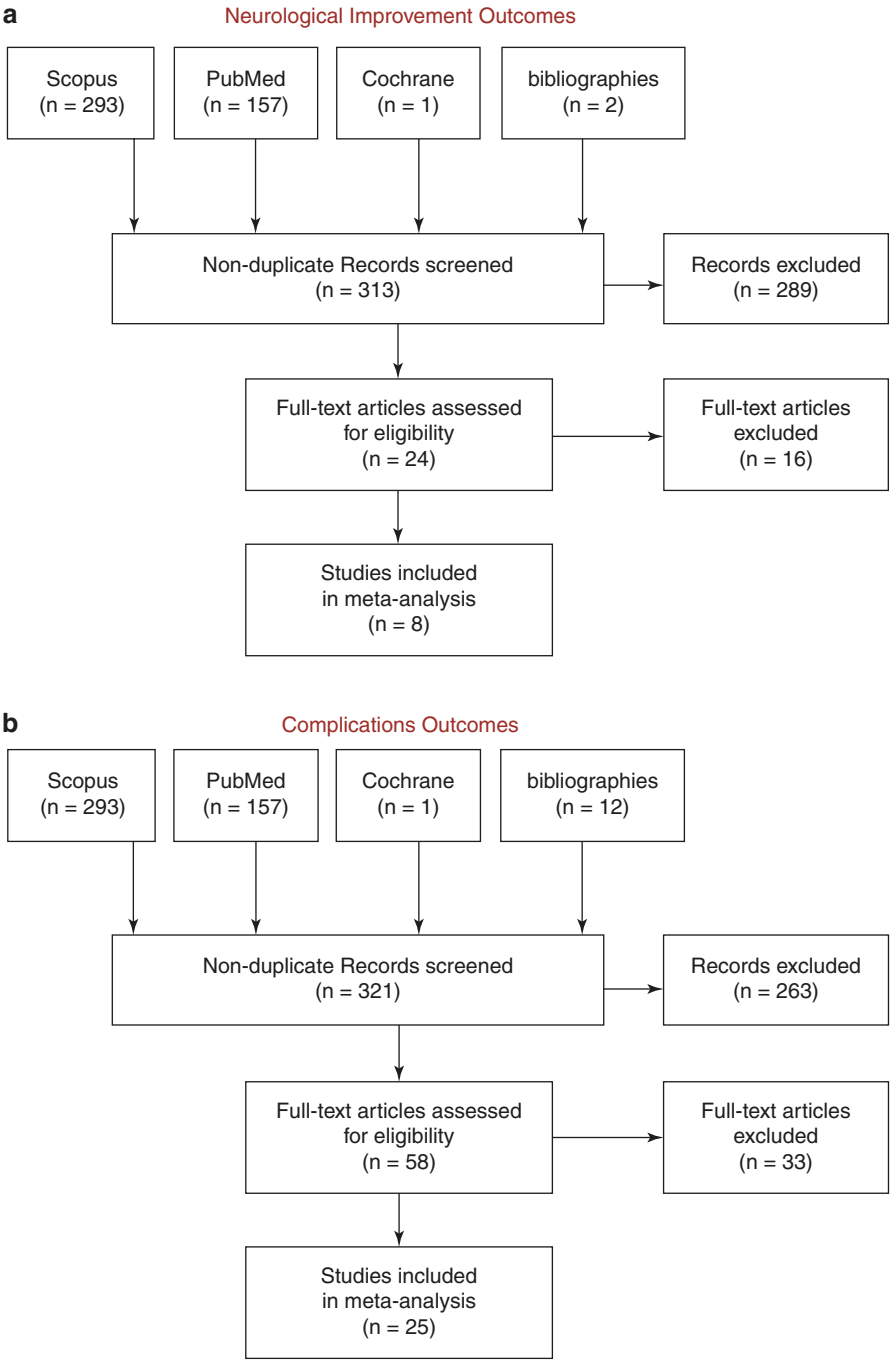

Fig. 3.1 (**a**) PRISMA flow diagram for neurological improvement outcomes analysis. (**b**) PRISMA flow diagram for complications outcomes analysis

Table 3.1 Characteristics of included studies reporting neurological outcomes related to cranioplasty timing

Reference	Type	Level of evidence	Quality	Indication for DC	Location	Early CP (days)	Number of procedures	
							Early	Late
Bender et al. [24]	Cohort	4	7	ICH, ischemic stroke, SAH, SDH, TBI	Bifrontal, unilateral	86	75	72
Cho and Park [28]	Cohort	4	5	TBI	NR	42	15	21
Cong et al. [29]	Cohort	4	5	TBI	Unilateral	90[a]	22	55
Honeybul et al. [27]	Case series	4	7	ICH, infection, ischemic stroke, SAH, TBI, tumor	Bifrontal, unilateral	90	20	28
Huang et al. [26]	Case series	4	6	TBI	Bifrontal, bilateral, unilateral	90	76	29
Kuo et al. [30]	Case series	4	7	ICH, ischemic stroke, TBI	NR	90	7	6
Paredes et al. [25]	Cohort	4	7	AVM, ICH, infection, ischemic stroke, SAH, reabsorption, TBI	Bifrontal, unilateral	85	10	45
Zhang et al. [31]	Cohort	4	7	TBI	Unilateral	90	23	47
Totals							*248*	*303*
							551	

AVM arteriovenous malformation, *CP* cranioplasty, *DC* decompressive craniectomy, *ICH* intracerebral hemorrhage, *NR* not reported, *SAH* subarachnoid hemorrhage, *SDH* subdural hematoma, *TBI* traumatic brain injury

[a]Article reports individual case data or data at various time intervals. Patients were divided at a 90-day cutoff

studies with non-matched cohorts, with an OCEBM Level 4 evidence. Indications for initial craniectomy included arteriovenous malformations, ischemic or hemorrhagic stroke, infection, ruptured aneurysm, trauma, or tumors. Six of twenty-five studies dichotomized early and late cranioplasty at a time-point other than 90 ± 10 days (range 42–120 days), and the reported data did not allow for regrouping around 90 days [13, 14, 28, 42, 43, 49]. Six studies included only trauma patients [13, 28, 31, 36, 38, 46].

Neurological Outcome Measures

Multiple neurological assessment tools were used across included studies (Table 3.1). Four studies reported more than 1 assessment to evaluate neurological outcome [24, 28, 30, 31]. For pooled analysis, the "primary" measure was designated as whichever measure the study focused on; for all 4 studies this was Barthel Index (BI). The timing of neurological assessment evaluation varied among studies. Three studies did not provide pre-cranioplasty assessments. The remaining studies

Table 3.2 Characteristics of included studies reporting complications related to cranioplasty timing

Reference	Indication for DC	Location	Early CP cutoff (days)	Number of patients		Complications
				Early	Late	
Archavlis et al. [34]	ICH, infection, ischemic stroke, rupture aneurysm, TBI	Unilateral	90[a]	147	53	Complication
Bender et al. [24]	ICH, ischemic stroke, ruptured aneurysm, TBI	Bifrontal, unilateral	86	75	72	EDH, hydrocephalus, ICH, infection, ischemic stroke, local bone graft complication, seizure
Chang et al. [35]	AVM, elective AVM/aneurysm, ICH, infection, ischemic stroke, other, ruptured aneurysm, TBI, tumor		90[a]	89	119	Complication
Chaturvedi et al. [36][b]	TBI	Bifrontal, unilateral	90	20	54	Complication
Cheng et al. [37]	Arachnoid cyst, AVM, ICH, ischemic stroke, ruptured aneurysm, tumor, venous sinus thrombosis		90	41	43	Infection
Cho and Park [28]	TBI		42	15	21	Infection, subdural fluid collection, ventriculomegaly
Chun et al. [38]	TBI	Unilateral	90	30	15	Dural tear, infection, inadequate dissection, soft tissue injury, subdural fluid
Gooch et al. [39]	Infection, intraoperative swelling, stroke, trauma	Bifrontal, bilateral, unilateral	100	31	31	Complication, reoperation

Hng et al. [40][b]	Infection, ruptured aneurysm, stroke, TBI, tumor	Bifrontal, unilateral	90	121	66	Complication, contour irregularity, extra-axial collections requiring evacuation, infection requiring removal, superficial infection, postop shunting, resorption requiring removal, seizures
Im et al. [41]	TBI, tumor, vascular	Bifrontal, unilateral	90	84	47	Infection
Kim et al. [33]	Trauma, non-trauma		90[a]	76	35	Infection
Kim et al. [42]	ICH, infection, ischemic stroke, rupture aneurysm, TBI, tumor		60	23	83	Epidural fluid collection
Mukherjee et al. [43]	AVM, ICH, intracranial infection, infected bone flap, ischemic stroke, ruptured aneurysm, TBI, tumor	Bifrontal, unilateral	120	29	145	Complication, post-op length of stay, removal
Nagayama et al. [32]	ICH, ischemic stroke, ruptured aneurysm, TBI, other		90[a]	181	25	Infection
Paredes et al. [25][b]	AVM, ICH, ischemic stroke, reabsorption, ruptured aneurysm, TBI	Bifrontal, unilateral	85	10	45	Complication
Piedra et al. [13]	Stroke		70	37	37	Complication, hematoma, hydrocephalus, infection, resorption
Piedra et al. [13]	TBI		90[a]	78	79	Complication, hematoma, hydrocephalus, infection, resorption
Piitulainen et al. [44]	Infection, stroke, TBI		90	21	79	Reoperation

(continued)

Table 3.2 (continued)

Reference	Indication for DC	Location	Early CP cutoff (days)	Number of patients		Complications
				Early	Late	
Rosseto et al. [45]	Infection, TBI, tumor		85	18	27	Infection
Schuss et al. [14]	ICH, ischemic stroke, other, ruptured aneurysm, TBI	Bifrontal, unilateral	60	54	226	Abscess, cerebrospinal fluid fistula, EDH/SDH, hygroma, wound healing disturbance
Song et al. [46]	TBI	Unilateral	90	25	18	Infection, subdural fluid
Tsang et al. [47][b]	Cerebrovascular disease, infection, TBI, tumor		90[a]	60	102	Flap depression, infection
Walcott et al. [48][b]	Stroke, TBI	Convexity, bifrontal, bilateral convexity	90	71	168	Infection, seizure, wound healing disturbance, surgical site infection, hydrocephalus, hematoma
Yang et al. [49]	ICH, ischemic stroke, SAH, TBI, tumor		60	62	68	Infection
Zhang et al. [31]	TBI	Unilateral	90	23	47	Epilepsy, infection, perioperative meninges breakdown, postoperative fluid below skin flap, wound healing
Totals				*1421*	*1705*	
				3126		

AVM arteriovenous malformation, *CP* cranioplasty; *DC* decompressive craniectomy, *EDH* epidural hematoma, *ICH* intracerebral hemorrhage, *OCEBM* Oxford center for evidence-based medicine, *SAH* subarachnoid

[a]Article reports individual case data or data at various time intervals. Patients were divided at a 90-day cutoff

[b]Data obtained via correspondence with author

performed assessments within 1 week preceding cranioplasty. Postcranioplasty assessments ranged from 72 h to over 6 months after the procedure [24, 26, 27, 31]. The following neurological measures were reported in the included studies. The Glasgow Coma Score (GCS) is an assessment of mental status typically used in acute trauma management. The Glasgow Outcome Score (GOS) categorizes cognitive disability following head injury, ranging from 1 (death) to 5 (resumption of normal life). The Karnofsky Performance Scale (KPS) was originally designed to assess the functional status of patients with cancer to determine if they could endure chemotherapy treatment. It ranges from 0 to 100, with values over 70 indicating relative functional independence in carrying out normal activities of daily living (ADLs) [50]. The BI is a more granular assessment of a patient's ability to perform each of 10 ADLs. It ranges from 0 to 100, with higher scores indicating higher functional independence [51–53]. The Function Independence Measure (FIM) evaluates disability in spinal cord injury, assessing both motor and cognitive performance. It ranges from 0 to 126, with higher scores indicating more independence [54, 55].

Change in Pre- and Postcranioplasty Neurological Status

Regardless of timing, improvement in neurological outcome was observed after cranioplasty [24, 25, 27, 29–31]. Pooling the results across studies, using only the primary measure (BI) for the two studies with multiple measures, showed cranioplasty at any time being significantly associated with improvements in neurological outcome (SMD 0.56; CI 0.11–1.01; calculation not shown in Figures).

Pre-cranioplasty, there was no significant difference in baseline neurological score between early cranioplasty and late cranioplasty groups in the 7 studies reporting pre- and post-cranioplasty scores, except for the study reporting KPS [24, 25, 27–31]. The KPS study by Cong et al., had lower baseline neurological score pre-cranioplasty in the early cranioplasty group compared to the late cranioplasty group (SMD –0.46; CI: −0.96–0.04). On all individual neurological outcome measures in those 7 studies, early cranioplasty was favored over late cranioplasty for greater neurological improvement from pre- to post-cranioplasty but was only statistically significant in the Karnofsky Performance Status measure (SMD: 7.22; CI: 5.95–8.49) (Table 3.3, Fig. 3.2). There was significant heterogeneity across outcomes

Table 3.3 Summary of findings of effect of early versus late cranioplasty after decompressive craniectomy on neurological improvement

	Number of patients				
Outcome	No. of studies	Early cranioplasty	Late cranioplasty	Relative effect (95% CI)	GRADE certainty of the evidence
Barthel index	4	115	170	SMD 2.51 (−0.76–5.78)	Very low due to inconsistency
Karnofsky performance status	1	22	55	SMD 7.22 (5.95–8.49)	Low
Functional independence measure	2	95	100	SMD 2.77 (−2.14–7.68)	Very low due to inconsistency
Glasgow coma scale	1	7	6	SMD 1.20 (−0.02–2.42)	Very low due to small sample size

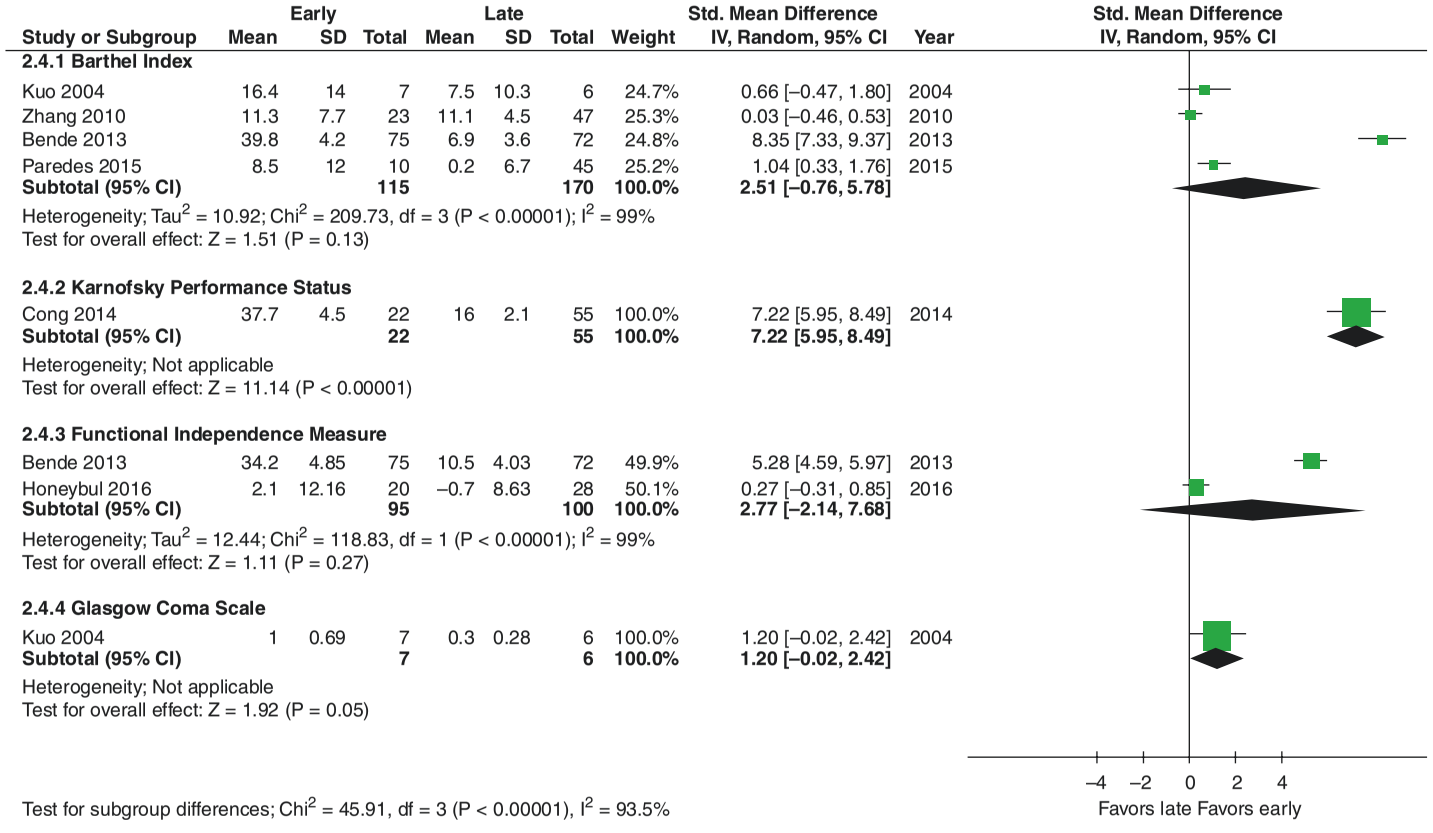

Fig. 3.2 Forest plot of studies reporting both pre- and post-procedure neurological scores for early and late cohorts. The early cohort showed greater improvement in every measure, and both KPS (SMD 7.22) and the overall pooled primary measures showed significant improvement (SMD 2.9, see text). *Reprinted with permission* [12]

($I^2 = 93.5\%$). Pooling the results across studies, using only the primary measure (BI) for the two studies with multiple measures, revealed early cranioplasty being associated with significant improvements in neurological outcome (SMD 2.90; CI 0.46–5.34; calculation not shown in Fig. 3.2).

Complications

Complications from cranioplasty after decompressive craniectomy reported in the literature included infections (18 studies), complications requiring reoperation (11 studies), intracranial hemorrhage (6 studies), extra-axial fluid collections (5 studies), hydrocephalus (6 studies), seizures (4 studies), and bone resorption (3 studies) (Tables 3.2 and 3.4).

There was no significant difference in the odds of overall complications between the early cranioplasty group and the late cranioplasty group looking at the trauma group (OR 0.74, 95% CI 0.30–1.83) or the mixed group (OR 1.24, 95% CI 0.92–1.66) (Fig. 3.3). There was also no significant difference when specifically looking at infection (Trauma: OR 0.46, CI 0.17–1.23; Mixed: OR 1.38, CI 0.96–1.99), reoperation (Trauma: OR 0.52, CI 0.18–1.47; Mixed: OR 0.82, CI 0.57–1.18), intracranial hemorrhage (Trauma: OR 3.12, CI 0.32–30.66; Mixed: OR 0.64, CI 0.33–1.23), seizures (Trauma: OR 0.67, CI 0.07–6.79; Mixed: OR 1.02, CI 0.50–2.11), or resorption (Trauma: OR 0.78, CI 0.35–1.79; Mixed: OR 1.23, CI 0.36–4.24). There was a significantly lower odds of developing a non-hemorrhagic extra-axial fluid collection with early cranioplasty in the trauma group (OR 0.24, CI 0.07–0.88) but not in the mixed group (OR 1.56, CI 0.69–3.53). The odds of developing hydrocephalus was significantly higher with early cranioplasty in both the trauma group (OR 4.99, CI 1.00–24.88) and the mixed group (OR 2.03, CI 1.01–4.07).

Level of Evidence

Neurological Outcome

All studies included in assessing neurological outcome as a function of cranioplasty timing were observational in design. To date, there are no randomized control trials related to this that are found in the literature and therefore the quality of evidence is low by GRADE standards. As these are all observational and retrospective, it is highly likely that those who were selected for an earlier versus later cranioplasty had significantly different clinical characteristics beyond the commonly controlled factors (e.g. age, gender) that may have led to the surgeons to perform the cranioplasty at a preferred time. These characteristics were likely to be more favorable, such as earlier resolution of swelling, in the early cranioplasty group. This would decrease the strength of any conclusions that can be made about the timing.

There were 4 different measures of neurological outcome across the 8 studies. We therefore had to look at these measures as different outcomes with consideration to overall trends. The level of evidence was further decreased to “very low” for the

Table 3.4 Summary of findings for effect of early versus late cranioplasty after decompressive craniectomy on complication rate by indication

Complication	Number of patients				
	No. of studies	Early Cranioplasty	Late Cranioplasty	Relative effect (95% CI)	GRADE certainty of the evidence
Complications, any					
Trauma subgroup	6	191	234	OR 0.74 (0.30–1.83)	Very low due to inconsistency
Mixed subgroup	19	1230	1471	OR 1.24 (0.92–1.66)	Low
Infection					
Trauma subgroup	2	108	94	OR 0.46 (0.17–1.23)	Low
Mixed subgroup	12	895	924	OR 1.38 (0.96–1.99)	Low
Reoperation					
Trauma subgroup	1	78	79	OR 0.52 (0.18–1.47)	Low
Mixed subgroup	9	592	696	OR 0.82 (0.57–1.18)	Low
Intracranial hemorrhage					
Trauma subgroup	1	78	79	OR 3.12 (0.32–30.66)	Low
Mixed subgroup	5	358	569	OR 0.64 (0.33–1.23)	Low
Non-hemorrhagic extra-axial fluid collection					
Trauma subgroup	3	70	54	OR 0.24 (0.07–0.88)	Low
Mixed subgroup	2	77	309	OR 1.56 (0.69–3.53)	Low
Hydrocephalus					
Trauma subgroup	2	93	100	OR 4.99 (1.00–24.88)	Low
Mixed subgroup	4	304	343	OR 2.03 (1.01–4.07)	Low
Seizures					
Trauma subgroup	1	23	47	OR 0.67 (0.07–6.79)	Low
Mixed subgroup	3	267	306	OR 1.02 (0.50–2.11)	Low
Resorption					
Trauma subgroup	1	78	79	OR 0.78 (0.35–1.79)	Low
Mixed subgroup	2	158	103	OR 1.23 (0.36–4.24)	Low

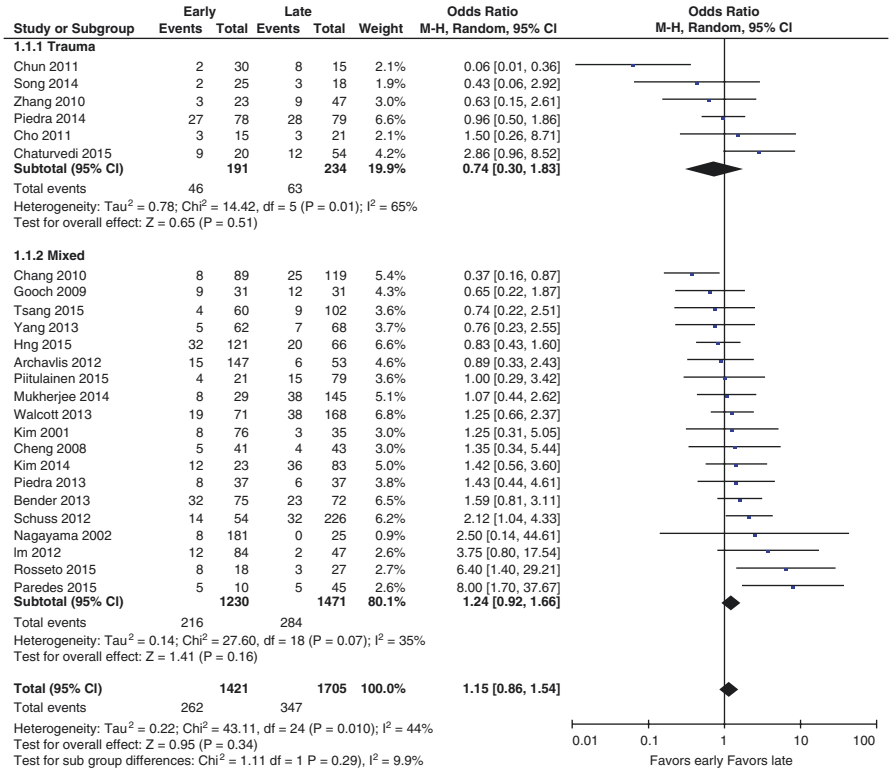

Fig. 3.3 Forest plot of studies reporting overall complications with early or late cranioplasty stratified by population type (trauma versus mixed). The blue square data markers indicate odds ratios (ORs) from primary studies, with sizes reflecting the statistical weight of the study using random-effects meta-analysis. The horizontal lines indicate 95% confidence intervals (CIs). The diamond data markers represent the subtotal and overall OR and 95% CIs. The vertical solid line indicates the line of no effect (OR 1). Results indicate no difference in odds of overall complications with early cranioplasty. *Reprinted with permission* [18]

BI and FIM outcomes due to very high heterogeneity among their included studies. The KPS and GCS outcomes only had 1 study each. The GCS outcome was based on a small sample of 13 patients and therefore also was graded "very low" due to imprecision.

Complications

The studies in the assessment of complication outcomes were similarly all retrospective and observational. Also similarly, we do not know if the patients who received early cranioplasty had significant characteristics that were different from the late cranioplasty group. To separate the effect of the initial indication for decompressive craniectomy on complication rate, the analysis and evidence was compiled separately for traumatic and mixed indications.

All outcomes had low quality of evidence by GRADE standards due to being only observational studies. The overall complication outcome in the trauma group was further rated down to very low due to inconsistency as measured by I^2 for heterogeneity between studies.

Patient Preferences

Considering the effect of earlier versus later cranioplasty timing after decompressive craniectomy on both neurological outcome and complications, there is insufficient evidence to strongly recommend one approach routinely over the other. The risks and benefits comparing early versus late cranioplasty is presented in Table 3.5.

Cranioplasty after decompressive craniectomy is associated with neurological improvement regardless of timing, with a potentially better outcome with early cranioplasty based on limited evidence.

There are risks to undergoing cranioplasty regardless of timing. These including hemorrhage (bleeding), infection, bone resorption, hydrocephalus, non-hemorrhagic extra-axial fluid collection, and seizures. There is limited evidence which suggests that the probability of certain complications differs by timing, with earlier cranioplasty being associated with increased risk of hydrocephalus and later cranioplasty being associated with increased risk of extra-axial fluid collection if there was a traumatic cause for the initial craniectomy.

Discussion

There has been no consensus on the ideal timing for cranioplasty after decompressive craniectomy. Several factors contribute to the desired interval before cranioplasty. These include the optimal timing to derive the most neurological improvement and the greatest reduction in complications.

After decompressive craniectomy has been performed to relieve the acute problem of elevated intracranial pressure, there are biological changes that can arise from altered cerebral hemo- and hydrodynamics. These changes specifically include

Table 3.5 Summary of risks and benefits comparison to guide patient preferences

	Early cranioplasty after decompressive craniectomy	Late cranioplasty after decompressive craniectomy
Benefits	Neurological improvement	
	Potentially better neurological outcome than later cranioplasty	
Risks	Bleeding, infection, bone resorption, hydrocephalus, extra-axial fluid collection, seizures	
	Possible increased risk of hydrocephalus compared to later cranioplasty	Possible increased risk of extra-axial fluid collection compared to earlier cranioplasty if craniectomy was for a traumatic indication

altered cerebrospinal fluid dynamics which can lead to hydrocephalus and pseudomeningoceles, increased perfusion in response to inflammation, and hypoperfusion in the long term [56–58]. Beyond providing better cosmesis through subsequent cranioplasty, it also likely helps by reducing the level of these changes or restoring the dynamics to a state closer to the pre-injury state [30, 59–62]. Though not the focus of this chapter, this is likely the reason why cranioplasty, regardless of timing, is associated with neurological improvement [63–65].

Neurological Outcome

Neurological improvement was measured by different measures in the reviewed studies. There is no commonly accepted measure for assessing neurological improvement after cranioplasty, though BI was the most common measure in our review. BI and FIM addresses both cognitive and motor performance. GCS also addresses cognitive function, but is likely too simple and not as sensitive to small improvements such as BI. Due to the differences in measures and the different indications for decompressive craniectomies, there was very high heterogeneity in the analysis of neurological improvement even with reporting of standard mean difference.

Early cranioplasty is likely to provide better neurological improvement outcomes based on the most recent studies. All included studies, except for 2, had similar neurological scores pre-cranioplasty between early and late cranioplasty groups [25, 31]. The improvement post cranioplasty was greatest in the study using the KPS measure with a SMD of 7.22 (CI 5.95–8.49) [29]. When pooling all neurological measures for overall improvement, there was still statistically significant improvement in the early cranioplasty group over the late cranioplasty group (SMD 2.90; CI 0.46–5.34) even though the separate subgroups measuring BI, FIM, and GCS were trending toward, but not significantly favoring, early cranioplasty. The large SMD of the KPS study likely contributed to the overall statistical significance. Additionally, there was a high degree of heterogeneity among subgroups (I^2 93.5%) which suggests that caution must be taken when interpreting these findings.

We did not separate our analyses in the assessment of neurological improvement by initial indication for decompressive craniectomy. The benefits of early or late cranioplasty may differ based on this factor and if so, the recommendations will need to be specific for this. Further studies with separate analysis based on initial pathology such as trauma, infection, or hemorrhage are therefore warranted.

Complications

Early cranioplasty after decompressive craniectomy is more likely to have associated hydrocephalus than late cranioplasty. In the trauma subpopulation, later cranioplasty is more likely to develop associated extra-axial fluid collection than early cranioplasty. With the potential benefits of more neurological improvement with early

cranioplasty, the findings taken together suggest that early cranioplasty is preferred over late cranioplasty. This would require more expectant management and observation for hydrocephalus. For trauma populations, the benefit of early cranioplasty may be greater due to the decreased risk of extra-axial fluid collection as well.

The literature describes a wide range of complication rates, partly due to the types of complications reported. From our review, the overall complication rate after cranioplasty is 19.5%. The pooled rate of infection was 8.1% with no significant difference in odds of infection between early and late cranioplasty in the trauma and mixed groups. The study by Rosseto et al. found a significant increased odds of infection with early cranioplasty but also found other factors that may play role which includes having the cranioplasty in the same hospitalization as the decompressive craniectomy, having a recent systemic infection before cranioplasty, neurological deficits as evaluated by a low GCS or motor deficits, and lower levels of hemoglobin [45].

Reoperations, not including placement of a ventriculoperitoneal shunt for hydrocephalus, were a common complication at 12.9% but there was no significant difference in odds between early and late cranioplasty in the trauma or mixed groups. Though the odds of reoperation appeared to favor early cranioplasty (OR 7.8, CI 0.55–1.10), this may have been due to bias in selecting patients who have less severe pathology for earlier cranioplasty.

We found a 4.6% rate of intracranial hemorrhage with no difference between early or late cranioplasty in the trauma and mixed groups. A previous study by Zanaty et al. found that other factors such as gender (male), race (African American), and hypertension are associated with an increased risk for intracranial hemorrhage [66].

We found a 13.9% rate of non-hemorrhagic extra axial fluid collections. This was largely due to high percentage of this complication in both early and late cranioplasty reported in Kim et al. study [42]. In the mixed group, which included the study by Kim et al. there was no significant difference between early and late cranioplasty. There was a significantly lower odds of extra-axial fluid collection with early cranioplasty in the trauma group. It may be postulated that in an early cranioplasty, the space between the cranioplasty flap and the brain is less but increased when edema further decreases at later time points.

There was an overall 6.0% rate of hydrocephalus. The odds of hydrocephalus with early cranioplasty were increased in both the trauma group (OR 4.99, CI 1.00–24.88) and the mixed group (OR 2.03, CI 1.01–4.07). The evidence suggests that patients with existing hydrocephalus should be considered at an increased risk for hydrocephalus but interestingly delaying cranioplasty in this subgroup can also increase the risk of persistent hydrocephalus [67]. The cause of the hydrocephalus is therefore not easily attributed to initial insult, decompressive craniectomy, or subsequent cranioplasty. If there is no pre-existing hydrocephalus, there might be a benefit to delaying cranioplasty due to the increased odds with early cranioplasty in trauma and mixed groups.

We found a 6.1% rate of seizures after cranioplasty with no difference between early or late cranioplasty in the trauma and mixed groups.

The overall rate of bone resorption was 10.8% with no difference in odds by timing in either the trauma or mixed groups. There are literature reporting higher rates of resorption in the pediatric population [68, 69]. We do not know if younger age in the adult population is associated with increased rate of resorption as well and if age has an interaction with timing for cranioplasty. There is evidence that the presence of a ventriculoperitoneal shunt is associated with increased resorption [17].

Limitations

The definition of early and late for cranioplasty is most frequently whether before or after 90 days. This is an artificial date but commonly used in studies and so is what is most reflected in our results. There may be more significant differences in neurological benefits or complication rates that are more noticeable at different time cut-offs. In the complication rate analysis, five studies used different time points for early and late other than before or after 90 days [14, 28, 42, 43, 49]. Therefore the time point at which the benefits and risks begin to be significantly different may be different that the conventional 90 days or may not follow a simple early/late classification. Regardless, the existing studies provide some direction to surgeons when deciding between several factors on when is the ideal time to perform the cranioplasty.

The research findings on cranioplasty timing both on neurological improvement and rate of complications are limited by the low quality of evidence. We are therefore unable to make strong recommendations, but due to the lack of contrary evidence, the findings may be useful to surgeons and patients. Perhaps the most significant limitation is the absence of any randomized controlled trials in the review. All studies identified were retrospective observational studies. Without randomization, we are unable to control for selection bias which was highly likely. Patients selected for early cranioplasty may have had less severe injury or earlier resolution of pathology that were clinically important but not accounted for in the analysis, e.g. degree of swelling on imaging, trauma versus ischemic stroke versus hemorrhage. In assessing neurological outcomes, unlike complications, it is possible to perform pre- and post-procedure assessments using the same neurological function measure. While there was no overall difference, two studies had different baseline neurological function between groups, with the late cranioplasty group having better scores at baseline in the Paredes et al. study whereas the early cranioplasty group had better baseline scores in the Zhang et al. study [25, 31]. Therefore, in addition to other clinical indicators, there might have been neurological function differences at baseline between the early and late cranioplasty groups. Only randomized studies with consistent measurement timing and long term follow-up can answer these questions.

Even though all neurological outcome studies tended towards favoring early cranioplasty, the high degree of heterogeneity among subgroups of separate neurological outcome measures and in the pooled analysis is another limitation. The studied population also had variation in type of injury as the evidence for neurological improvement is not separated by initial indication for decompressive craniectomy (e.g. trauma versus stroke versus hemorrhage). The pooled analysis is a combination of four different measures with different sensitivities and specificities for neurological improvement. The evidence base will be strengthened if the studies used more comprehensive measures as BI or FIM and separate analyses based on initial indication for decompressive craniectomy. Studies using GCS and GOS appear too coarse.

Conclusion

Within the limited evidence, we suspect that early cranioplasty (within 90 days) after decompressive craniectomy is a safe option. Though surgeons should be aware of a potentially greater risk for hydrocephalus, it is likely to provide better neurological improvements. Taking the results from the analyses together, this would make early cranioplasty the preferred option over later cranioplasty.

Box Summary

1. What is known?
   Cranioplasty after decompressive craniectomy is associated with neurological improvement regardless of timing. There are several complications associated with cranioplasty after decompressive craniectomy which include hemorrhage, infection, reoperation, hydrocephalus, extra-axial fluid collection, bone resorption, and seizures.
2. What is new?
   Early cranioplasty (within 90 days) after decompressive craniectomy may provide more neurological improvement but may increase the risk of hydrocephalus compared to later cranioplasty. In the trauma population, early cranioplasty may be associated with decreased risk of non-hemorrhagic extra-axial fluid collection.
3. What are the consequences for clinical practice?
   Further research with prospective clinical trials are recommended for better quality evidence on the timing of cranioplasty after decompressive craniectomy on neurological improvement and complication rate. Pending ongoing and future research, surgeons should consider early cranioplasty (within 90 days) as potentially preferable to later cranioplasty for better neurological improvement with anticipatory management of increased risk of hydrocephalus.

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