Early Cranioplasty is Associated with Greater Neurological Improvement: A Systematic Review and Meta-Analysis

James G. Malcolm, PhD[‡*]
Rima S. Rindler, MD[‡*]
Jason K. Chu, MD, MS[‡]
Falgun Chokshi, MD[§]
Jonathan A. Grossberg, MD[‡]
Gustavo Pradilla, MD[‡]
Faiz U. Ahmad, MD, MCh[‡]

[‡]Department of Neurological Surgery, Emory University, Atlanta, Georgia; [§]Department of Radiology, Emory University, Atlanta, Georgia

*These authors contributed equally to this work.

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Correspondence:
Faiz Ahmad, MD, MCh,
Emory Faculty Office Building,
49 Jesse Hill Drive SE,
Room #341,
Atlanta, GA 30303.
E-mail: faiz.ahmad@emory.edu

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BACKGROUND: Cranioplasty after decompressive craniectomy is a common neurosurgical procedure, yet the optimal timing of cranioplasty has not been well established.
OBJECTIVE: To investigate whether the timing of cranioplasty is associated with differences in neurological outcome.
METHODS: A systematic literature review and meta-analysis was performed using MEDLINE, Scopus, and the Cochrane databases for studies reporting timing and neurological assessment for cranioplasty after decompressive craniectomy. Pre- and postcranioplasty neurological assessments for cranioplasty performed within (early) and beyond (late) 90 d were extracted. The standard mean difference (SMD) was used to normalize all neurological measures. Available data were pooled to compare pre-cranioplasty, postcranioplasty, and change in neurological status between early and late cranioplasty cohorts, and in the overall population.
RESULTS: Eight retrospective observational studies were included for a total of 528 patients. Studies reported various outcome measures (eg, Barthel Index, Karnofsky Performance Scale, Functional Independence Measure, Glasgow Coma Scale, and Glasgow Outcome Score). Cranioplasty, regardless of timing, was associated with significant neurological improvement (SMD .56, $P = .01$). Comparing early and late cohorts, there was no difference in precranioplasty neurological baseline; however, postcranioplasty neurological outcome was significantly improved in the early cohort (SMD .58, $P = .04$) and showed greater magnitude of change (SMD 2.90, $P = .02$).
CONCLUSION: Cranioplasty may improve neurological function, and earlier cranioplasty may enhance this effect. Future prospective studies evaluating long-term, comprehensive neurological outcomes will be required to establish the true effect of cranioplasty on neurological outcome.

KEY WORDS: Cranioplasty, Timing, Neurological outcome, Barthel Index, Karnofsky Performance Status, Functional Independence Measure, Glasgow outcome scale, Glasgow coma scale

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Cranioplasty after decompressive craniectomy is a commonly performed neurosurgical procedure aimed at restoring cranial cosmesis, cerebral protection, and facilitating neurological rehabilitation.[1,2]

ABBREVIATIONS: ADLs, activities of daily living; **BI,** Barthel Index; **CI,** confidence interval; **FIM,** Function Independence Measure; **GCS,** Glasgow Coma Score; **GOS,** Glasgow Outcome Score; **KPS,** Karnofsky Performance Scale; **OCEBM,** Oxford Center for Evidence-Based Medicine; **PRISMA,** Preferred Reporting Items for Systematic Reviews and Meta-Analyses; **SMD,** standard mean difference

Cranioplasty, although considered routine by many, can be associated with significant morbidity.[3-6] The interval between craniectomy and cranioplasty has received considerable attention as a potential modifiable risk factor.[7-11] Surgeons traditionally have waited several months before cranioplasty to allow the patient to recover from the primary neurological insult and to ensure that cerebral edema and inflammation resolve,[12] although earlier cranioplasty increasingly has been advocated as a viable, low-risk option that may enhance neurological outcome.[1,13-18]

The purpose of this study was to (1) evaluate the effect of cranioplasty on neurological function and (2) to determine whether the timing on cranioplasty affects this neurological change. To answer these questions, a systematic review of the literature was performed to compare the neurological outcomes of patients undergoing early versus late cranioplasty after craniectomy.

METHODS

Search Strategy

A systematic review of the literature adherent to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines was performed for published articles reporting on timing of cranioplasty after craniectomy.[19] PubMed/MEDLINE, Scopus, and the Cochrane databases were searched using the keywords "cranioplasty, early" or "cranioplasty, timing" included in the title, abstract, or keyword list. The search was restricted to original clinical studies published between January 1990 and April 2016 using either autologous bone or synthetic implants. Thorough bibliographic searches of qualifying articles and relevant medical journals were also performed to identify additional articles for inclusion.

Study Selection

Articles reporting on the relationship between timing of cranioplasty after decompressive craniectomy and quantitative, standardized neurological outcomes of human adults were included in the analyses. Case-control studies, cohort studies, or clinical trials were included. Case series that reported enough raw timing and neurological assessment data to allow authors to make the necessary computations for at least 10 patients were also included. Case reports, technical notes, letters, and editorials were excluded. Reviews were also excluded; however, referenced articles were thoroughly screened for possible inclusion. Studies that involved animals, included noncalvarial or maxillofacial procedures, or focused exclusively on the pediatric population were excluded.[20] Studies were excluded if a significant proportion of patients underwent nondecompressive craniectomy (eg, for resection of skull tumor). For articles that mentioned collecting timing or neurological assessment data but did not report it, attempts were made to contact authors for further details and potential inclusion. The search results were independently screened by 2 authors (JM and RR); disagreements were resolved by consensus.

Study quality of individual articles was determined by using the Oxford Center for Evidence-Based Medicine (OCEBM) guidelines.[21] Risk of bias was assessed by the Newcastle-Ottawa Scale, which is a 3-category, 9-point scale assessing cohort selection, comparability, and outcome, with a higher score indicating higher quality.[22]

Data Extraction

The following data were extracted from each article, if reported: number of patients, indication for initial craniectomy, time interval between craniectomy and cranioplasty, and pre- and postcranioplasty neurological assessment.

Data Analysis

Data were analyzed using Review Manager 5.3.5 (The Cochrane Collaboration, London, United Kingdom). All but 1 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 d. While arbitrary, we followed this convention in our analysis: "early" cranioplasty was defined as less-than-or-equal-to 90 d after craniectomy, "late" was defined as beyond 90 d. Case series 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 d, 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. The overall effect of cranioplasty on neurological outcome was first assessed by analyzing the change in pre- and postcranioplasty scores across all patients regardless of timing. This was then repeated for early and late cranioplasty groups. The pooled mean and standard deviation was used for this calculation. The pooled standard deviation is calculated as $([n_1-1]s_1^2+[n_2-1]s_2^2)/(n_1+n_2-2)$ for the standard deviations of each group (early s_1, late s_2) and the size of those groups (n_1,n_2). Change in pre- and postcranioplasty scores was also 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 standard deviation of the difference in sample means is approximately equal to $\mathrm{sqrt}(s_1^2/n_1 + s_2^2/n_2)$ for standard deviations (s_1,s_2) and counts (n_1,n_2).

The pre-cranioplasty neurological status of early and late cranioplasty groups was then compared to determine preoperative similarity between the 2 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.

For studies reporting multiple neurological assessment tools, only the primary measure was included in the combined analysis. Studies were grouped according to neurological assessment tool for subgroup analysis. SMD calculations were pooled using the Mantel-Haenszel method with random-effects model due to the heterogeneity of different measures included. The I^2 metric was used to quantify heterogeneity (0% = no heterogeneity, 100% = maximal heterogeneity).[23] The Chi^2 test was used to evaluate significant differences between subgroups. *P*-values less than .05 were considered statistically significant.

RESULTS

Literature review results are shown in the PRISMA flow diagram (Figure 1). Three hundred thirteen nonduplicate studies were screened. This included 311 articles from the database search and 2 additional articles identified from bibliographic review. Sixteen articles were excluded after full-text review. Reasons for exclusion were as follows: review article, lack of craniectomy-to-cranioplasty timing data,[4,18,24-30] cranioplasties all either within or beyond 90 d,[31-34] significant proportion of nondecompressive craniectomies,[12] qualitative data,[18] insufficient data (ie, authors unreachable or unable to provide).[13,32,33,35,36] Thirteen authors were contacted for further information regarding missing data.[13-15,17,18,30,32,33,35–39] Five of these authors were able to provide data not included in the original publication that allowed inclusion in this analysis.[14,15,38-40] Two studies included

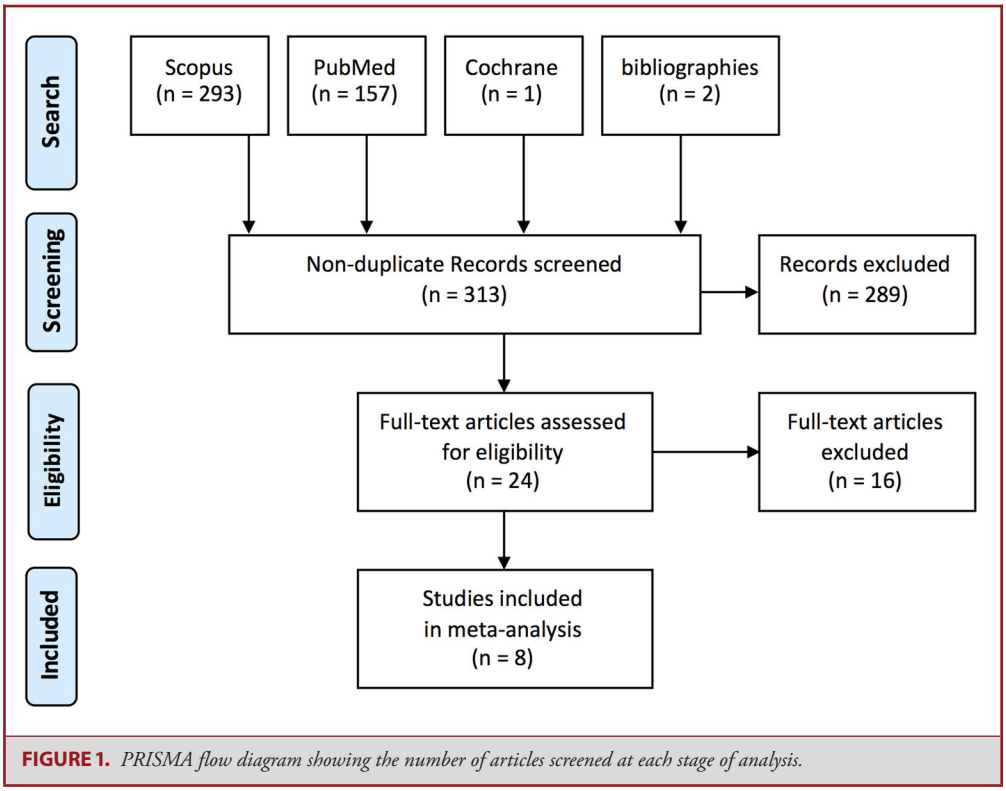

FIGURE 1. *PRISMA flow diagram showing the number of articles screened at each stage of analysis.*

duplicate patients; the more recent and larger study was included in the analyses.[39,40]

The final 8 included studies represent 551 cranioplasty procedures (248 early, 303 late). Table 1 lists individual study characteristics. Table 2 combines and summarizes these characteristics across studies. 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 (Table 2). Four studies included only trauma patients.[17,30,37,38] Cranial procedure locations, when specified, included unilateral, bilateral, and bifrontal. One study dichotomized early and late cranioplasty at 42 d and did not report data to allow regrouping around 90 d.[37] All other studies were dichotomized within 1 week of the 90-d threshold.

Multiple neurological assessment tools were used across included studies (Table 3). Four studies reported more than 1 assessment to evaluate neurological outcome.[14,17,37,41] For pooled analysis, the "primary" measure was designated as whichever measure the study focused on; for all 4 studies this was Barthel Index (BI) as indicated in Table 3. The timing of neurological assessment evaluation varied among studies. Three studies did not provide pre-cranioplasty assessments. The remaining studies performed assessments within 1 week preceding cranioplasty. Postcranioplasty assessments ranged from 72 h to over 6 mo after the procedure.[14,17,38,39]

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).[42] 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.[43-45] 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.[46,47]

Study quality ranged from 5 to 7 out of 9 on the Newcastle-Ottawa Scale (Table 1). None had matched cohorts, which significantly increases the risk of selection bias. Three studies were case series design, but the provided data could be divided and analyzed according to cranioplasty timing; study quality was assessed as if they were a cohort design.[38,39,41] All but 3

TABLE 1. Characteristics of Included Studies Reporting Neurological Outcomes Related to Cranioplasty Timing

Reference	Type	Level of Evidence	Quality	Indication for DC	Location	Early CP (d)	Number of Procedures	
							Early	Late
Bender et al, 2013[14]	Cohort	4	7	ICH, ischemic stroke, SAH, SDH, TBI	Bifrontal, unilateral	86	75	72
Cho et al, 2011[37]	Cohort	4	5	TBI	NR	42	15	21
Cong et al, 2014[30]	Cohort	4	5	TBI	Unilateral	90[a]	22	55
Honeybul et al, 2016[39]	Case Series	4	7	ICH, infection, ischemic stroke, SAH, TBI, tumor	Bifrontal, unilateral	90	20	28
Huang et al, 2013[38]	Case Series	4	6	TBI	Bifrontal, bilateral, unilateral	90	76	29
Kuo et al, 2004[41]	Case Series	4	7	ICH, ischemic stroke, TBI	NR	90	7	6
Paredes et al, 2015[15]	Cohort	4	7	AVM, ICH, infection, ischemic stroke, SAH, reabsorption, TBI	Bifrontal, unilateral	85	10	45
Zhang et al, 2010[17]	Cohort	4	7	TBI	Unilateral	90	23	47
					Totals		248	303
							551	

[a]Article reports individual case data or data at various time intervals. Patients were divided at a 90-d cutoff.
AVM = arteriovenous malformation, CP = cranioplasty, DC = decompressive craniectomy, ICH = intracerebral hemorrhage, NR = not reported, SAH = subarachnoid hemorrhage, SDH = subdural hematoma, TBI = traumatic brain injury.

TABLE 2. Neurological Assessment Tools used by Each Study and the Timing of Assessment Relative to Cranioplasty

Patient Characteristics	
Early	248 (45%)
Late	303 (55%)
Total	551
Indication for craniectomy	
Trauma	430 (78.0%)
Ischemic stroke	52 (9.4%)
Subarachnoid hemorrhage	27 (4.9%)
Intracerebral hemorrhage	26 (4.7%)
Infection	8 (1.5%)
Arteriovenous malformation rupture	3 (.5%)
Subdural hematoma	3 (.5%)
Resorption	2 (.4%)
Tumor	2 (.4%)

studies included pre-cranioplasty functional scores.[30,37,38] Time to last follow up ranged from 3 d to 6 mo after cranioplasty (Table 3).

Change in Neurological Score Regardless of Timing

Seven studies reported both pre- and postcranioplasty neurological scores including BI (4 studies; 285 patients, 115 early, 170 late),[14,15,17,41] KPS (1 study; 77 patients, 22 early, 55 late),[30] FIM (2 studies; 195 patients, 95 early, 100 late),[14,39] and GCS (1 study; 13 patients, 7 early, 6 late).[41]

Combining early and late procedures, there were significant improvements in BI (SMD .45; confidence interval [CI; .14, .76]; $P = .005$) and KPS (SMD 1.57; CI [1.21, 1.93]; $P < .001$) measures after cranioplasty (Figure 2). Other outcome measures showed similar improvements, but these did not reach statistical significance (FIM .44, GCS .67). There was significant heterogeneity across subgroups ($I^2 = 86.8\%$, $P < .001$), suggesting cranioplasty may affect various neurological domains differently.

Two of these studies included multiple measures,[14,41] and including only the primary measure for each (BI, see Table 3), the pooled result across subgroups showed that cranioplasty was associated with significant improvements in neurological outcome across all time points and outcome measures (SMD .56; CI [.11, 1.01]; $P = .01$; not shown in Figure 2).

Pre-cranioplasty Neurological Baseline

Seven studies reported pre-cranioplasty neurological scores including BI (4 studies; 285 patients, 115 early, 170 late),[14,15,17,41] KPS (1 study; 77 patients, 22 early, 55 late),[30] FIM (2 studies; 195 patients, 92 early, 100 late),[14,39] and GCS (2 studies; 49 patients, 22 early, 27 late)[37,41].

There was no overall difference in neurological baseline between early and late cranioplasty groups across all measures (Figure 3). Two individual studies showed significant differences between early and late groups before cranioplasty, with the early group having a higher baseline in 1 study[17] and a lower baseline

TABLE 3. Summary Characteristics of Included Studies

Study	Pre-CP Assessment (days before CP)	Post-CP Assessment (days after CP)
Bender et al, 2013[14]	BI[ab], FIM[a], CRS[c] (<7)	BI[ab], FIM[a], CRS† (161.7±68.3)
Cho et al, 2011[37]	BI, GCS (0)	BI (30)
Cong et al, 2014[30]	KPS, NIHSS[c] (7)	KPS, NIHSS[c] (30)
Honeybul et al, 2016[39]	FIM[a], COGNISTAT[c] (0)	FIM[a], COGNISTAT[c] (<3)
Huang et al, 2013[38]	None	GOS[a] (>180)
Kuo et al, 2004[41]	BI[b], GCS, Muscle Power[c] (not reported)	BI[b], GCS, Muscle Power[c] (12.5±2.8)
Paredes et al, 2015[15]	BI[a], NIHSS[c] (7)	BI[a], NIHSS[c] (<3)
Zhang et al, 2010[17]	BI[b], KPS (<30)	BI‡ (30), KPS (180)
Totals		
Glasgow Coma Scale	2	1
Glasgow Outcome Score	0	1
Karnofsky Performance Scale	1	2
Barthel Index	4	5
Functional Independence Measure	2	2

Data reported as "mean ± std dev" where appropriate.
[a]Data obtained via correspondence with author.
[b]Primary measure used for overall pooled analysis in studies reporting more than one measure.
[c]Not included in quantitative analysisBI = Barthel Index, CP = cranioplasty, COGNISTAT = Neurobehavioral Cognitive Status Examination, CRS = Coma Remission Scale, FIM = Functional Independence Measure, GCS = Glasgow Coma Scale, GOS = Glasgow Outcome Score, KPS = Karnofsky Performance Scale, NIHSS = NIH Stroke Scale.

in the other study.[15] There were no significant differences among subgroups (I^2 = 0%, P = .46). There was significant heterogeneity in effect within the 4 studies reporting BI (I^2 = 72%, P = .01).

Two studies reported multiple measures,[14,41] and including only the primary measure for each (BI, see Table 3), the pooled result across subgroups showed no overall difference between precranioplasty baselines for early and late groups (SMD = –.09, CI [-.42, .25], P = .61; not shown in Figure 3).

Postcranioplasty Neurological Outcome

All 8 studies reported postcranioplasty neurological scores including BI (5 studies; 321 patients, 130 early, 191 late),[14,15,17,37,41] KPS (2 studies; 147 patients, 45 early, 102 late),[17,30] FIM (2 studies; 195 patients, 95 early, 100 late),[14,39] GCS (1 study; 13 patients, 7 early, 6 late),[41] and GOS (1 study; 105 patients, 76 early, 29 late).[38]

Only for the KPS subgroup was there a significant difference with early cranioplasty having higher postoperative outcome scores (SMD .91; CI [.27, 1.55]; P = .006; Figure 4). GCS could not be evaluated due to zero standard deviation in the early group.[41] All other subgroups showed a tendency for better outcomes in the early group but none reached significance (BI .69, FIM .39, GOS .08). There was no significant difference among assessment subgroups (I^2 = 41%, P = .17). Similar to preoperative scores, BI and FIM had significant heterogeneity among postoperative scores (I^2 = 87%, P < .01)

Three studies provided multiple postcranioplasty measures,[14,17,41] and after including only the primary measure for each study (BI, see Table 3), the pooled result across subgroups shows that early cranioplasty was associated with significantly better neurological outcomes (SMD .58; CI [.04, 1.13]; P = .04; not shown in Figure 4).

Change in Pre- and Postcranioplasty Neurological Status

Returning to the 7 studies that reported both pre- and postcranioplasty scores, early cranioplasty was associated with significantly greater improvements in KPS (SMD 7.22; CI [5.95, 8.49]; P < .001; Figure 5). All other measures showed greater improvements after early cranioplasty, but none reached significance (BI 2.51, FIM 2.77, GCS 1.20). Again, there was significant heterogeneity across subgroups (I^2 = 93.5%, P < .001), which was likely due to the disproportionate changes seen in early cranioplasty groups from Bender et al.[14]

Two of these studies included multiple measures,[14,41] and including only the primary measure for each (BI), the pooled result across subgroups showed that early cranioplasty was associated with significant improvements in neurological outcome across all assessment measures (SMD 2.90; CI [.46, 5.34]; P = .02; not shown in Figure 5).

DISCUSSION

The results of this literature review revealed that cranioplasty after decompressive craniectomy is associated with improved neurological function and that early cranioplasty may further enhance recovery. There is limited quality evidence on quantitative neurological outcomes and the timing of cranioplasty;

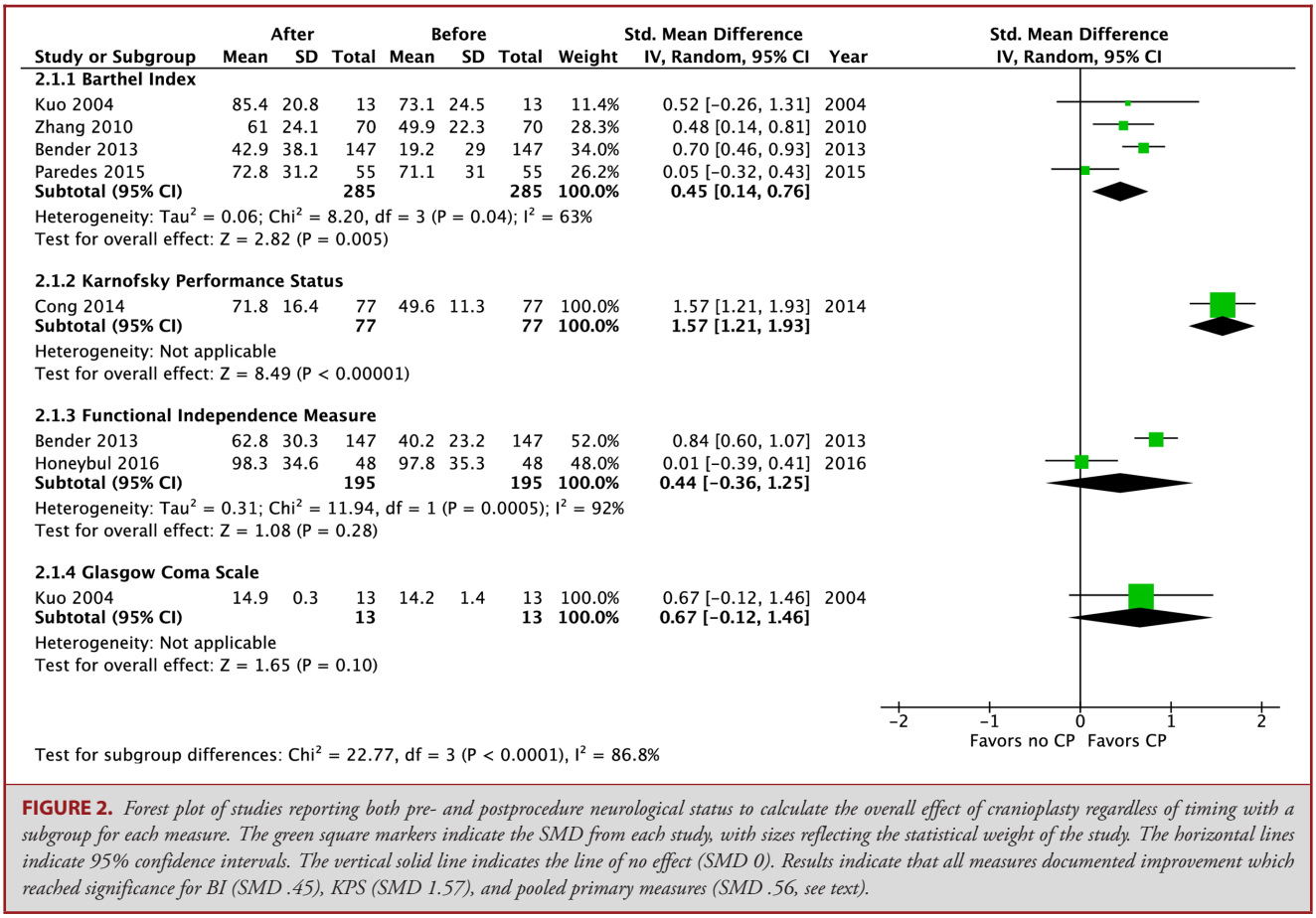

FIGURE 2. *Forest plot of studies reporting both pre- and postprocedure neurological status to calculate the overall effect of cranioplasty regardless of timing with a subgroup for each measure. The green square markers indicate the SMD from each study, with sizes reflecting the statistical weight of the study. The horizontal lines indicate 95% confidence intervals. The vertical solid line indicates the line of no effect (SMD 0). Results indicate that all measures documented improvement which reached significance for BI (SMD .45), KPS (SMD 1.57), and pooled primary measures (SMD .56, see text).*

all studies included in this review were retrospective in design and OCEBM Level 4 evidence. We found no randomized controlled trials examining the relationship of cranioplasty timing with regard to neurological outcomes, complications, or any other factors; however, one European trial addressing these exact questions appears to be underway.[48] Early cranioplasty has similar complication rates to cranioplasty performed at later time points,[10,11] but any advantage for improving neurological outcomes has yet to be uniformly studied. It is clear from the studies included in this review that there is heterogeneity in choice of neurological assessments and time to follow-up among other factors, which makes generalization of these findings difficult; however, the overall effect of cranioplasty and its timing remain clear. Further, this review revealed several factors to inform future prospective studies.

Neurological Outcome Measures

An optimal outcome assessment for evaluating cranioplasty outcomes has not been established. A variety of outcome tools were utilized across studies, but no study justified the use of a particular measure. The most basic outcome assessments were GCS, GOS, and modified Rankin score, which may have been chosen for ease of obtaining the data from chart reviews. KPS quantifies a patient's general ability to carry out activities of daily living, but BI is likely a more sensitive tool for this purpose because of its finer scale. BI was the most common measure used across studies (n = 5/8). Similar to BI, FIM addresses motor performance but also cognitive performance, which is a unique feature. The use of standard mean difference provided some normalization in the analyses; however, there was significant heterogeneity in each analysis, likely because they address a few neurological domains in populations with complex neurological derangements across multiple domains.

Furthermore, these outcome tools were applied to heterogeneous populations espousing a number of etiologies for neurological injury. The tools were developed and validated for use in specific populations (eg, GOS for trauma, mRS for ischemic stroke, KPS for oncology patients, etc.), although they are often applied to various other populations. This nonselective use of outcome measures may affect the accuracy and sensitivity with which they can identify postcranioplasty changes. Additionally, not all studies evaluated pre- and postcranioplasty outcomes. Some applied different assessment tools pre-and postcranioplasty, and others used multiple tools postcranioplasty.[14,39,41] An ideal

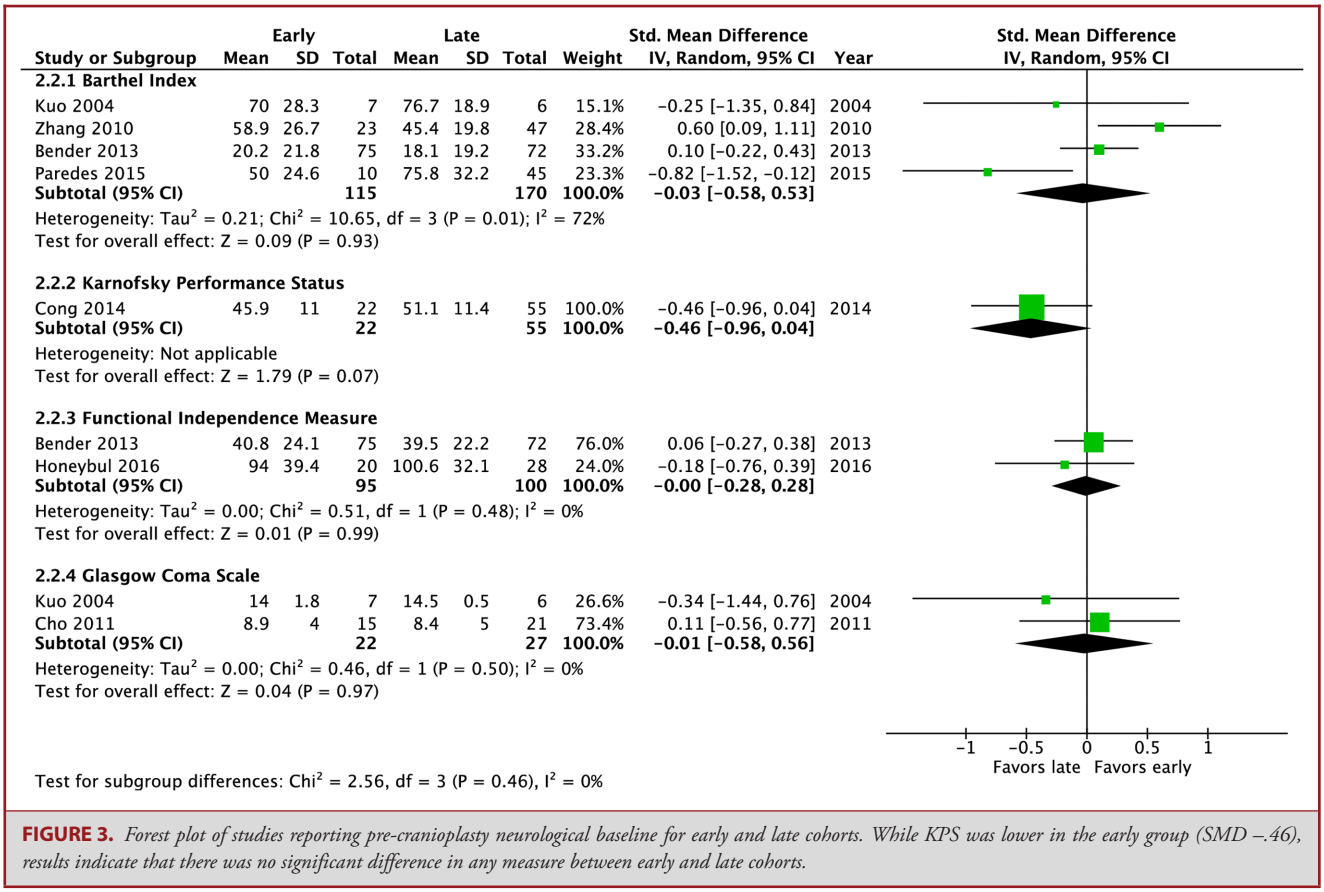

FIGURE 3. *Forest plot of studies reporting pre-cranioplasty neurological baseline for early and late cohorts. While KPS was lower in the early group (SMD –.46), results indicate that there was no significant difference in any measure between early and late cohorts.*

outcome measure would include multiple neurological domains (ie, physical, functional, cognitive, and emotional), would be applied before and after the procedure at fixed time points, and would be utilized for their respective validated populations. This would likely improve the chances of identifying the specific neurological changes associated with cranioplasty.

Cranioplasty is Associated with Neurological Improvement

In this review, patients had improved neurological outcome regardless of cranioplasty timing. Complications and neurological function follow a predictable temporal pattern in the wake of decompressive craniectomy.[6,49,50] In the initial days to weeks, patients are at greatest risk for complications from their primary neurological insult. Once the initial inflammatory process recedes several weeks later, hydrocephalus and pseudomeningoceles may begin to develop from altered cerebrospinal fluid dynamics. Patients may begin to recover neurologically during this period, but may go on to develop headaches, irritability, epilepsy, discomfort, and even psychiatric symptoms associated with a sunken flap.[1,6,50] Cranioplasty during this period has been shown to improve these symptoms,[36,51,52] likely by restoring the normal cerebral hemo- and hydrodynamics[18,25,26,41]. Following craniectomy there may be a period of increased perfusion possibly due to inflammatory factors. As this resolves, parenchymal hypoperfusion develops, which may be related to the neurological decline. After cranioplasty, perfusion dynamics are restored.[26] One study in our review found a strong correlation between ipsilateral middle cerebral artery velocity and BI after cranioplasty suggesting that improved hemodynamics are necessary for improved neurological function.[41]

In our analysis, cranioplasty at any time is associated with significant neurological improvement. Notably, the largest improvements were found in 2 studies with the longest follow up (5-6 mo)[14,17], whereas the remaining studies showed more moderate improvements at follow-up within 30 d. This is consistent with one series that found no significant perioperative change in GCS but did find differences over a longer time horizon which they attributed to gradual recovery from primary injury.[51] It is difficult from available data to decipher how much of this improvement results from effects of the cranioplasty procedure or general recovery from neurological injury; however, it is clear that long-term follow-up is necessary to appreciate the fullest extent of recovery.

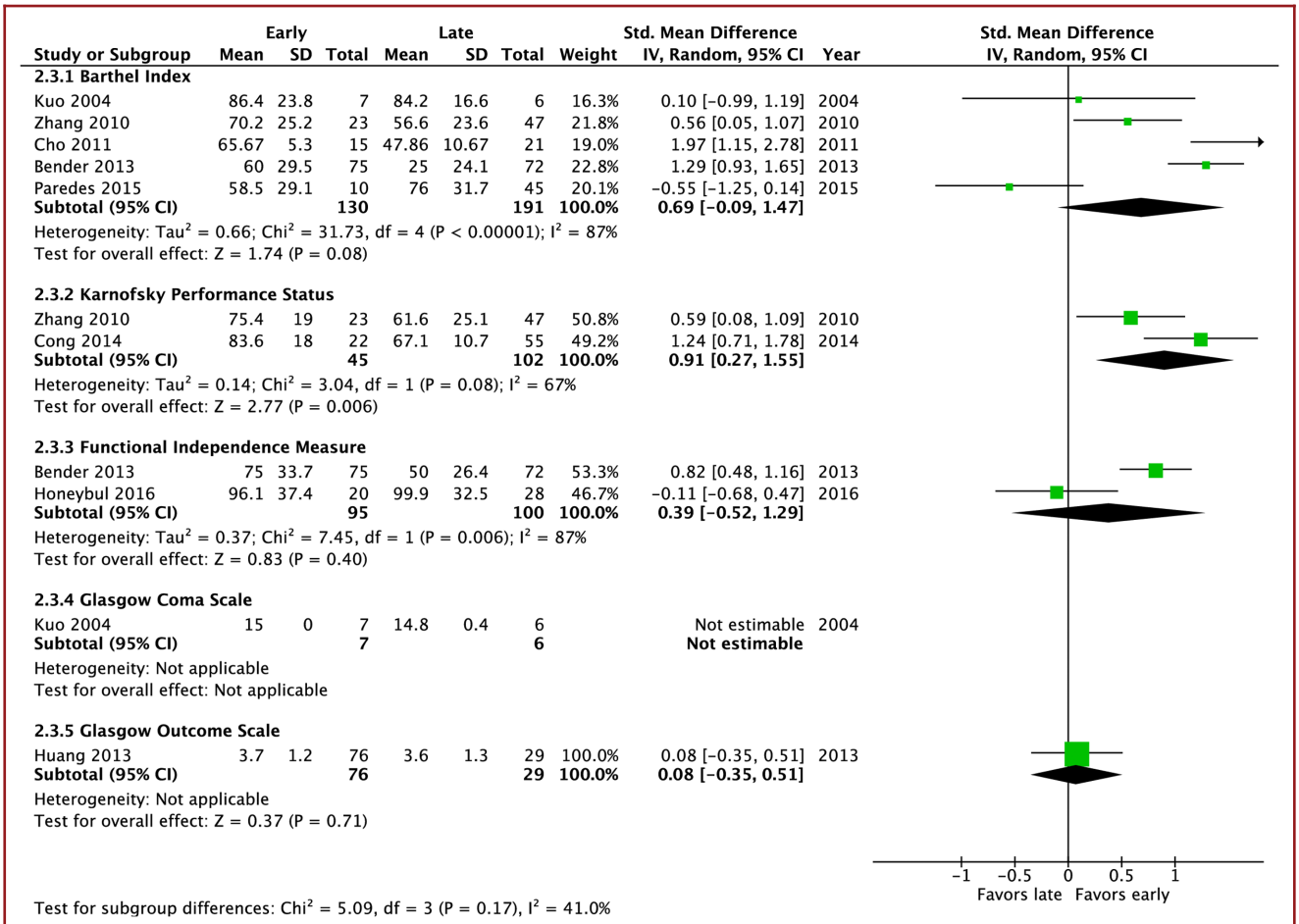

FIGURE 4. *Forest plot of studies reporting postprocedure neurological outcome for early and late cohorts. Results indicate that the early cohort showed improved BI (SMD .69) and FIM (SMD .39) scores and significant improvement in KPS score (SMD .91). Overall pooled primary measures showed significant improvement (SMD .58, see text).*

Early Cranioplasty is Associated with Greater Neurological Improvement

In this analysis, early cranioplasty was associated with improved overall neurological outcome, and greater change in neurological status after cranioplasty. There was no difference in preoperative assessment scores between early and late cranioplasty groups, indicating a similar baseline neurological status. Early cranioplasty was associated with better pooled neurological outcomes across all outcome measures (SMD 0.58, $P = .04$), largely influenced by a single study measuring KPS (SMD .91, $P = .006$). As a caveat, 2 studies had significantly different neurological baselines between early and late groups prior to cranioplasty.[15,17] While these pooled findings are strong, there was significant heterogeneity in each separate analysis, suggesting significant variability across the population using each measure. Two additional studies not eligible for inclusion in the current review support the above findings.[13,35] Although neither study explicitly controlled for preoperative baseline status, both found that cranioplasty beyond 90 d was associated with worse clinical outcomes (defined as proportion of patients with GOS 1–3). Further, cranioplasty within 42 d had better outcomes than those between 42 and 90 d (GOS 4-5 78% vs 46%).[13] In contrast, a study included in this review noted greatest improvement in BI if cranioplasty was performed within 60 to 90 d, with no additional benefit if performed before 60 d.[14] BI may be a more sensitive tool for discriminating the optimal time for a procedure, but this has yet to be confirmed.

There is no agreed-upon definition of an "early" cranioplasty time-point, and many studies use different time points. Previous case series have reported favorable neurological outcomes (GOS 4 or 5) in 67% to 74% of patients undergoing cranioplasty within 3 mo,[32,34] both other studies have used different time points (eg, 42 d,[37] 90 d,[14,15,17,35,53] analyzing at multiple time-points[13,30]). Other investigations have treated time as a continuous variable in

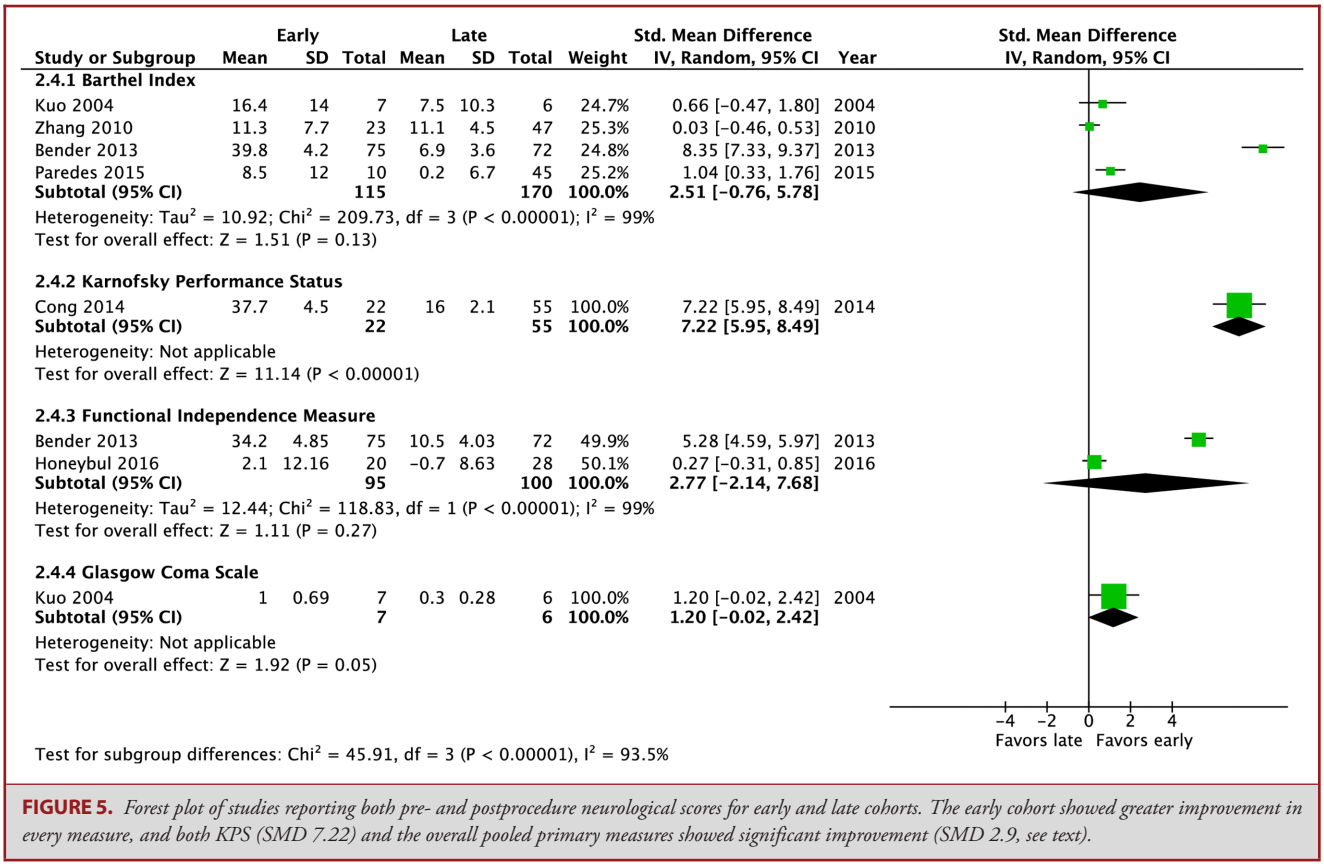

FIGURE 5. *Forest plot of studies reporting both pre- and postprocedure neurological scores for early and late cohorts. The early cohort showed greater improvement in every measure, and both KPS (SMD 7.22) and the overall pooled primary measures showed significant improvement (SMD 2.9, see text).*

risk factor regression analysis,[39] used nonparametric rank tests,[35] or attempted to fit a curve relating timing and functional score.[30] Among the studies included in our analysis, all but one were dichotomized around 90 d.[37] This time-point was chosen out of convenience for ease of pooling data across studies. "Early" cranioplasty may, in fact, be the earliest time point after the edema from the initial neurological insult resolves, but this is likely different for individual patients or pathology. Future studies would ideally evaluate different time points to identify the optimal time for cranioplasty for different initial pathology (hemorrhage vs ischemic stroke vs trauma vs infection), possibly identify patient-specific biomarkers to monitor, or examine milestones in neurological recovery suitable for cranioplasty.

Among the studies included, several findings bear mention. In an attempt at greater resolution of timing of cranioplasty, one study looked at intervals of within 60 d, 60 to 90, 90 to 120, and beyond 120, and they found that BI was best in the 60 to 90 d interval while within 60 d conferred no additional benefit with higher variation.[14] Another study using FIM noted that while most had little to moderate improvement with early cranioplasty, some patients improved dramatically and that these improvements were more often in the cognitive domain rather than motor, both of which are assessed by FIM.[39] One predictive model in another study estimated that a patient had a 70% chance of improving at least 5 points in BI if cranioplasty was performed within 85 d.[15] Such findings, although preliminary, can help guide a surgeon in advising families about ideal timing of cranioplasty and the expected outcomes following the procedure.

Limitations

This study has important limitations. All included studies were retrospective and observational in design. No randomized controlled trials were available. Although the overall pre-cranioplasty neurological baselines were equal, 2 of the 8 studies had significantly different baselines between early and late groups (Figure 3).[15,17] It is possible that the early groups had improved outcome after cranioplasty simply because they were not as severely injured as the patients in the late groups. Additionally, there may be selection bias at play for choosing patients for earlier procedures. For example, patients who were showing signs of early recovery might have been chosen for earlier procedures, and subsequently appeared to have improved postcranioplasty outcome. While this study begins to lay the groundwork for this question, retrospective case-controlled trials or prospective randomized controlled trials are

required to establish an equal baseline between comparative groups.

Several aspects of this study showed heterogeneity. First, a variety of neurological outcome measures were used. While this led to heterogeneity among effects in each analysis, the overall trends remain clear. As mentioned, measures such as GCS, GOS, and KPS are likely not sensitive enough, and we suggest that future studies use more discriminating measures such as BI or FIM. A second source of heterogeneity is the underlying population and indication for decompression (Table 1). The largest subgroup was trauma (78%, n = 430/551) with vascular cases making up most of the remainder. It is likely that the initial indication may dictate the timing of cranioplasty and future studies should perform subgroup analysis. The timing of postprocedure assessment was an additional factor of variance among the included studies ranging from days to months (Table 3). Given that the greatest improvements were seen many months after cranioplasty, studies that had relatively short follow-up times might not be capturing peak recovery. In this present study there was little we could do to minimize the above variation beyond focusing on a primary neurological assessment scale from each study with appropriate follow-up and variation between cohorts. To minimize heterogeneity in future studies, we recommend using more comprehensive neurological measures, subgroup by primary pathology, and use longer follow-up.

In an effort to dichotomize timing events into early and late, the 90-d cutoff used in the included studies was arbitrary. Timing is likely best treated as a continuous variable to better evaluate optimal cranioplasty timing, as this may vary for different patient populations. Further, there may be patient-specific biomarkers or neurological recovery milestones that may be better for determining timing. Additionally, practical factors, such as staff availability or scheduling, may delay the procedure on the order of weeks after the decision has been made decision to proceed with cranioplasty, although it is unclear whether a variation of several weeks is significant enough to affect outcome.[14]

CONCLUSION

This systematic review and meta-analysis of the literature confirms that cranioplasty is associated with significant, quantifiable neurological improvement, and further that early cranioplasty may lead to even greater improvements. Well-designed prospective studies evaluating long-term, comprehensive neurological outcomes will be required to establish the true effect of cranioplasty on outcome.

Disclosure

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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COMMENT

The authors have done a very nice job of reviewing the literature and providing a meta-analysis about the timing of cranioplasty after decompressive craniectomy.

They demonstrate what most of us have seen in our practices but have often not been able to quantify. The authors demonstrate a statistically improved neurological outcome with cranioplasty whether done early or late. Importantly, they show that this benefit is more clearly seen in the early cranioplasties than the late cranioplasties. This seems to be the case in cranioplasties with diverse underlying pathologies including both trauma and stroke.

There is likely a change in the cerebral dynamics that occurs with the absence of the bone flap. The extreme case is nicely described in the recent *Neurosurgery* article on the Syndrome of the Trephined.[1] The interplay of the atmospheric pressure and its effects on local metabolism can affect the underlying neuronal functioning. Cerebrospinal fluid flow through the cerebral interstitium and the role of cerebral glymphatic and lymphatic systems are areas of interest as they certainly are affected by the presence or absence of the bone flap.[2,3] The flow of metabolites and waste products through the interstitium is likely affected and this paper suggests that the earlier restoration to normality affects neurological outcome. It ultimately affects the local neuronal functioning. This paper sets the stage for future studies on the effects of early vs late cranioplasty on long term sequelae of head injury such as seizures or post-traumatic hydrocephalus.

Jeff W. Chen
Orange, California

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