Risk factors for the development of seizures after cranioplasty in patients that sustained traumatic brain injury: a systematic review

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Summary

Decompressive craniectomy (DC) is used for the treatment of posttraumatic brain injury raised intracranial pressure. Cranioplasty is a reconstructive procedure that restores the structural integrity of the skull following (DC). Seizures are a recognised complication of cranioplasty but its incidence and risk factors in TBI patients are unclear. Accurate prognostication can help direct prophylactic and treatment strategies for seizures. In this systematic review, we aim to evaluate current literature on these factors. A PROSPERO-registered systematic review was performed in accordance with PRISMA guidelines. Data was synthesised qualitatively and quantitatively in meta-analysis where appropriate.

A total of 8 relevant studies were identified, reporting 919 cranioplasty patients. Random-effects meta-analysis reveals a pooled incidence of post-cranioplasty seizures (PCS) of 5.1% (95% CI 2.6-8.2%). Identified risk factors from a single study included increasing age (OR 6.1, p = 0.006), contusion at cranioplasty location (OR 4.8, p = 0.015), and use of monopolar diathermy at cranioplasty (OR 3.5, p = 0.04). There is an association between an extended DC-cranioplasty interval and PCS risk although it did not reach statistical significance (p = 0.062).

Predictive factors for PCS are poorly investigated in the TBI population to date. Heterogeneity of included studies preclude meta-analysis of risk factors. Further studies are required to define the true incidence of PCS in TBI and its predictors, and trials are needed to inform management of these patients.

Keywords: neurotrauma; epilepsy; post-traumatic seizures

Key Points

- Seizures are a recognised complication of cranioplasty after TBI
- Meta-analysis shows estimated incidence of 5.1%
- Potential risk factors include age, contusions at cranioplasty site, monopolar diathermy, and DC-cranioplasty interval

Introduction

Traumatic brain injury (TBI) is a common neurosurgical presentation, with a variable clinical phenotype depending on the severity and anatomy of injury[1; 2]. A proportion of TBI patients develop uncontrollable raised intracranial pressure (ICP). In this group, an increasingly common surgical management option is decompressive craniectomy (DC), involving the removal of a bone flap to allow the brain to swell while relieving ICP[3; 4]. The removed flap may be stored in an abdominal pouch or a specialised refrigeration unit, or discarded depending on factors such as infection and surgeon preference[5; 6].

After acute swelling of the brain resolves, cranioplasty is performed to restore the integrity of the skull and cerebrospinal fluid dynamics[7]. It is also an important factor in restoring psychosocial functioning of the patient, and allowing subsequent rehabilitation. Depending on patient factors and surgeon preference, the skull may be reconstructed using the bone flap removed during DC (autologous), or synthetic materials such as polyetheretherketone (PEEK) and titanium[5; 8; 9]. The benefits and risks associated with different cranioplasty materials are an area of active ongoing research[8; 10]. Another variable that may be associated with complications is the DC to cranioplasty interval – although there is conflicting evidence on the nature of this relationship [11].

Seizures are a recognised complication of cranioplasty[4; 12]. While TBI itself is known to cause epilepsy in some patients[2; 13], increasing evidence suggests that

cranioplasty can also cause new-onset seizures[14]. Some patients may develop status epilepticus, a life-threatening condition that may require critical care admission, or epilepsy requiring long-term regular medication and associated lifestyle modification[15]. Therefore, understanding the factors that predispose TBI patients undergoing cranioplasty to having seizures can help inform decisions regarding perioperative prophylactic antiepileptic medications[16]. Furthermore, given that cranioplasty is often performed at a point when patients are safe for discharge or transfer from the neurosurgical unit, it is important that the potential for new onset seizures is appreciated by the wider healthcare team. Previously proposed risk factors for PCS have included increasing age, sex, severity of initial trauma, DC-cranioplasty interval, and the cranioplasty implant material[8; 17; 18]. This systematic review aims to define risk factors for the development of PCS and the incidence of PCS in TBI patients.

Methods

This systematic review was performed in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[19]. The protocol was registered on the PROSPERO database (CRD42017077310).

Search Strategy

A multi-database (Medline, EMBASE, Web of Science) search was performed by authors RS and MZ on 23/05/2018 for articles published at any time. Difference of opinion on study inclusion was settled by consensus between authors. The search terms used were ‘cranioplasty’ or ‘post-cranioplasty’ AND ‘seizure*’ or ‘epilep*’ or ‘fits’ AND ‘traumatic brain injury’ or ‘TBI’ or ‘head injury’. The bibliography of each relevant paper was subsequently screened to identify any additional articles.

Study Selection

Strict inclusion and exclusion criteria were defined prior to searching the literature. Inclusion criteria included (i) DC followed by cranioplasty in a TBI cohort, (ii) age>16, (iii) data on any risk factors such as age, gender, severity of TBI, DC-cranioplasty interval and cranioplasty material (**Table 1**).

Data Analysis

All included studies were evaluated with respect to patient demographics; injury-related factors (severity, radiological features); surgery-related factors (including peri-operative complications); DC-cranioplasty interval; incidence of seizures; timing of seizure onset in relation to cranioplasty; nature of seizures and the cranioplasty implant material used. Meta-analysis was conducted using OpenMeta-Analyst software[20]. The ROBINS-I tool was used by authors SM, FS and IB independently to assess the internal validity and risk of bias in each study[21]. The level of evidence of each study was defined using the 2011 Oxford Centre for Evidence-Based Medicine Levels of Evidence[22].

Table 1- study selection criteria

Inclusion Criteria	**Exclusion Criteria**
Patients underwent DC following traumatic brain injury	Published in a language other than English
Patients aged 16 or over at time of cranioplasty	Conference abstracts
Includes data on any of the following: • Age, gender • Severity of trauma (defined clinically or radiologically) • Presence of neurological deficit • DC to cranioplasty interval • Infection at any time point • Cranioplasty implant material	Underlying pathology other than TBI included such that TBI patients cannot be distinguished from the general cohort
Considers complications after cranioplasty including seizures	Paediatric patients included such that the adult population cannot be distinguished from the general cohort
Any full text article of any study type including case reports and case series	

Results

A total of ten studies met the selection criteria[3; 4; 12; 14; 18; 23-27]. Two of these studies[3; 12] were excluded after closer inspection due to duplication of data in another paper[23]. Therefore, a total of 8 studies were included for final evaluation (**Figure 1**)[19].

Study characteristics

Included studies were predominantly retrospective database reviews (n=6), one prospective cohort study, and one study reporting a mixture of retrospective and prospective data (**Table 2**). Two studies reported cranioplasty for any indication, but identified the cases of PCS within their TBI cohort[18; 26]. Some papers (n=5) reported only an incidence of PCS without any analysis of predictive factors[4; 18; 23; 26; 27], while remaining papers disaggregated the PCS cases from controls for factors such as baseline demographics, DC-cranioplasty interval and intra-operative techniques, allowing analysis of risk factors[14; 24; 25].

Figure 1- PRISMA flow diagram demonstrating the study selection process.

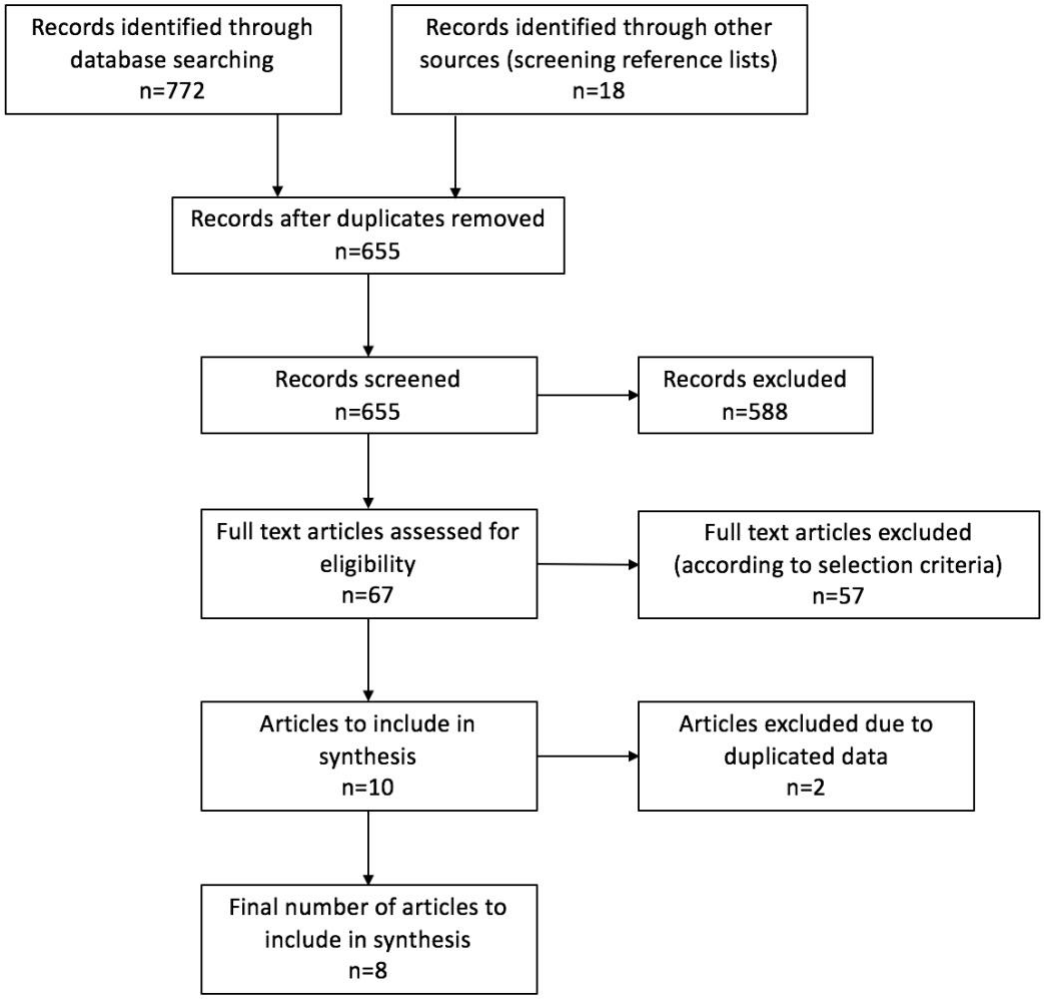

Records identified through database searching n=772
Records identified through other sources (screening reference lists) n=18
Records after duplicates removed n=655
Records screened n=655
Records excluded n=588
Full text articles assessed for eligibility n=67
Full text articles excluded (according to selection criteria) n=57
Articles to include in synthesis n=10
Articles excluded due to duplicated data n=2
Final number of articles to include in synthesis n=8

Table 2- Relevant data extracted from each included study. *indicates that these odds ratios are not given in the paper but calculated by the present authors from the data given. †note that the cut-off for early vs late cranioplasty is different between these papers. PCS: post-cranioplasty seizures, OR: odds ratio, CI: confidence interval, Ti: Titanium plate cranioplasty, FND: focal neurological deficit.

Study	Type	Number of patients	Number with PCS	Risk factors	OR (95% CI)	P-value
Broughton 2014	Retrospective database review	40	0	-	-	-
Honeybul 2014	Partly retrospective, partly prospective	230	19	-	-	-
Luo 2012	Retrospective database review	161	5	Manually-shaped Ti (vs computer-shaped)	0.70 (0.11-4.32)*	0.70
Pierson 2016	Retrospective database review	24	1	-	-	-
Songara 2016	Prospective cohort study	16	0	-	-	-
Stephens 2010	Retrospective database review	108	3	-	-	-

Wang 2017	Retrospective case-control study	270	32	Age >50	6.112 (1.956-19.099)	0.006
				Contusion at cranioplasty location	4.82 (1.414-17.432)	0.015
				Precranioplasty FND	0.258 (0.081-0.821)	0.019
				Artificial duraplasty (vs autologous fascia)	0.206 (0.626-14.441	0.007
				Use of monopolar diathermy	3.456 (1.067-9.732)	0.035
				Early cranioplasty (<6/12)†	0.359 (0.119-1.085)	0.062
Zhang 2010	Comparative analysis	70	4	Early cranioplasty (<3/12)†	0.681 (0.067-6.914)*	0.745
Total		919	64			

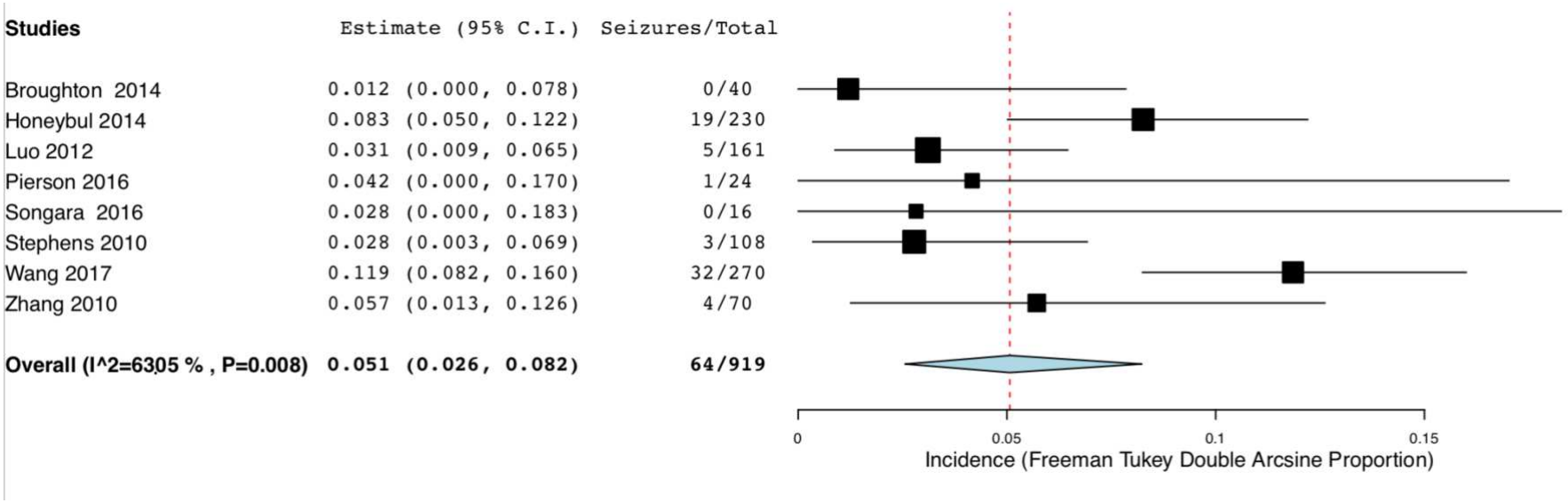
Patient cohort

In total, 919 patients who underwent cranioplasty following DC for TBI were reported. In studies reporting mean age (n=3), the average age was 39.1 years (448 patients)[4; 14; 25]. In studies reporting median age (n=2), the reported medians were 42 (40 patients)[26] and 30 (230 patients)[23]. Two studies reported only an age range of their patients, overall age 16-71 (177 patients)[24; 27]. One study reported age in its whole cohort of cranioplasty patients but did not report that of its TBI subgroup[18]. Five studies reported gender (625 patients), with 75.0% being male[4; 14; 24; 25; 27]. Few studies reported measures of TBI severity in their cohort of patients. Two studies reported mean Glasgow Coma Score (GCS) prior to cranioplasty, with an overall mean of 7.72 (86 patients)[25; 27]. One study reported mean GCS prior to initial DC in their cohort of 108 patients at 7.5[4]. The remaining studies (n=5) did not report baseline GCS or other parameters indicating TBI severity.

Incidence of PCS

Across included studies, 7.0% (64 out of 919 patients) developed new-onset seizures following cranioplasty. A random-effects meta-analysis was performed, demonstrating an overall estimate of PCS incidence at 5.1% (95% CI 2.6-8.2%) (see **Figure 2**). Only one paper (270 patients, 32 with PCS) reported the timing of new-onset seizures after cranioplasty, finding 37.5% occurred within 24 hours; 15.6% between 24 hours and seven days; and 46.8% more than seven days post-operatively[14].

Figure 2- Forest plot demonstrating the pooled incidence of PCS using the Freeman Tukey Double Arcsine Proportion in a random-effects model.



Risk factors

Three studies disaggregated the features of their PCS patients from controls, allowing for analysis of predictive factors[14; 24; 25]. Three studies investigated complication rates comparing early and late cranioplasty with respect to DC[14; 25; 27]. One study (16 patients) reported an absence of seizures within their one month follow up period, in both early and late cranioplasty groups[27].

While the other two studies did observe seizures in their cohorts, their defined cut-off between 'early' and 'late' cranioplasty was different, at three months[25] and six months[14], preventing meta-analysis. The first study (70 patients) compared the frequency of PCS in patients with DC-cranioplasty interval <3 months with those >3 months, and compared the effect of suturing the dura during DC. No significant difference was seen in frequency of PCS when comparing these groups[25]. The other study (270 patients) demonstrated a potential effect of late cranioplasty (>6 months) on PCS in multivariate analysis, but this did not reach statistical significance ($p=0.062$)[14]. In addition, this particularly increased risk of immediate and early (<7 days) seizures compared to late ones, but statistical significance was not reported[14].

One study (161 patients) compared the outcomes of two methods for shaping titanium plate used for cranioplasty in a non-randomised study[24]. The frequency of PCS was not significantly different between the computer-shaped and manually-shaped groups. Other studies (n=4) included patients with a mix of autologous, titanium and synthetic cranioplasty materials, but frequency of PCS in each subgroup was not delineated[4; 18; 23; 26].

One study (270 patients) employed a case-control design comparing PCS patients with healthy controls on multivariate analysis[14]. The significant independent predictive factors were age>50, contusion at location of cranioplasty, or focal neurological deficit prior to cranioplasty (**Table 2**). No significant effect of cranioplasty infection on PCS risk was seen (OR 3.01, 95% CI 0.626-14.441)[14].

Level of evidence and risk of bias

With respect to level of evidence, all included studies were level 4. Of included studies, five were at moderate risk of bias, two were at serious risk and one was low (see **Table 3**). Serious risk of bias was assigned to one study due to very short follow up time[27], and to another because it did not account for confounding between study groups, did not report follow up time and was unclear whether patients were randomly allocated to the different intervention groups[25]. The reasons for papers being assigned a moderate risk of bias was retrospective data collection, and a variable follow up time within their cohorts.

Table 3- Risk of bias assessments using the ROBINS-I tool.

Study	Overall risk of bias regarding PCS
Broughton 2014	Moderate
Honeybul 2014	Moderate
Luo 2012	Moderate
Pierson 2016	Moderate
Songara 2016	Serious
Stephens 2010	Moderate
Wang 2017	Low
Zhang 2010	Serious

Discussion

Seizures are an important complication after TBI, as well as after cranioplasty. Uncertainty remains regarding management of PCS and the provision of prophylactic anti-epileptic medication. In this systematic review, we aimed to investigate potential risk factors and the incidence of PCS in the TBI cohort of cranioplasty patients.

Incidence of PCS

Our meta-analysis demonstrates a PCS incidence of 5.1% in the TBI cohort of patients. Observed statistical heterogeneity and paucity of high quality, prospective studies with sufficient follow up periods affect the reliability of this estimate. Indeed, several recent prospective studies of PCS in cohorts of mixed underlying pathology have found incidences in the range 12.5-17.3%[8; 16; 28; 29]. However, these PCS incidence in the TBI cohort alone cannot be deduced from these studies. Also, several studies that investigate the complications of PCS do not explore the incidence of seizures[30-33]. This may reflect a lack of recognition of PCS as a procedural complication, or that seizures were not observed in these series. The incidence of post-traumatic seizures in severe TBI is 13.6%[2].

Patient Demographics

The demographic of the patient cohort in this review is consistent with the larger TBI population, with a male preponderance and an average age of approximately 40 years[34]. Only one included study examined the effect of age on PCS risk, demonstrating that age over 50 years was associated with greater risk in multivariate regression (OR 6.1)[14]. This association with increasing age has been reproduced in studies of PCS with mixed underlying pathology[17], and increasing age has been shown to increase risk of complications of cranioplasty in general[35]. Studies of cranioplasty patients with various underlying pathologies have demonstrated associations between male gender and risk of PCS[17; 36]. We did not find a similar effect in the TBI cohort, which may be a result of the male preponderance.

Severity of TBI

Current evidence suggests that severity of trauma is predictive of risk of post-traumatic seizures[2]. However, included studies did not provide sufficient details to allow analysis of the effect of severity of TBI on risk of PCS. Interestingly, Wang et al demonstrated that focal neurological deficit prior to cranioplasty was associated with a reduced risk of PCS[14]. In contrast, one study of cranioplasty patients with mixed underlying pathology demonstrated the opposite; presence of neurological deficit was associated with an increased risk of PCS[37]. Further studies are required to clarify (i) the relationship between severity of trauma and PCS, and (ii) whether neurological deficit correlates with risk of PCS in a pathology dependent manner. Also, Wang et al found that presence of cerebral contusion at the cranioplasty site increased risk of PCS[14]. It is known that patients with cerebral contusions and resulting neuroinflammation are at greater risk of post-traumatic seizures[38]. However, these findings suggest that the mechanical forces applied during the cranioplasty procedure itself could further increase risk of seizure activity originating at the site.

Timing of Cranioplasty

Our review suggests that a greater DC-cranioplasty interval is associated with an increased PCS risk[14; 25], although this did not reach statistical significance. This trend is consistent with other studies demonstrating an association between early cranioplasty and improved outcomes across several measures[27; 29]. One study explored the effect of cranioplasty timing on risk of complications in a mixed pathology cohort[39]. They demonstrated that risk of complications was maximal when cranioplasty was performed between 100 – 136 days following DC and fell after this timepoint. However, only one patient in this series suffered from PCS, experiencing status epilepticus after receiving the cranioplasty within 30 days of DC[39]. In contrast, a meta-analysis demonstrated no significant association between the length of delay prior to cranioplasty and the risk of PCS in patients with mixed underlying pathology[11]. Further studies are required to evaluate the relationship between DC-cranioplasty interval and risk of PCS in TBI patients.

Cranioplasty Implant Material

There are now a large variety of materials available for cranioplasty, including autologous bone, titanium sheet/mesh, polyetheretherketone (PEEK) and polymethylmethacrylate (PMMA). However, the benefits and risks associated with use of different materials in the TBI cohort remain to be evaluated. Four of the eight included studies performed cranioplasties with varying materials[4; 18; 23; 26]. None of these studies assessed the risk of post-cranioplasty complications with respect to implant material used. One study compared manually and computer-shaped titanium implants with respect to post cranioplasty complications[24]. There was no significant difference in PCS incidence between groups. The effect of implant material on post-cranioplasty complications is explored more extensively in the literature in the context of various underlying pathologies. Despite significant differences being observed in terms of risk of post-operative infection[9], differences in risk of PCS have not been demonstrated[8; 17; 42; 43].

Infection

Current evidence demonstrates a possible role for infection as a risk factor for PCS in mixed pathologies[17]. Of included studies, one study explored the relationship between infection at the cranioplasty site and PCS risk. Results demonstrated an adjusted OR 3.0, but failed to reach statistical significance on multivariate analysis. Hence, further studies are required to evaluate the effect of infection on PCS in TBI.

Timing of Seizures

Only one included study detailed the timing of PCS in relation to the cranioplasty[14]. Their data implies a bimodal distribution of PCS, with one peak in the first 24 hours and a second at over a week after cranioplasty, with less than 20% of the total occurring in the interim. Delayed cranioplasty particularly increased risk of 'immediate' and 'early' seizures (<24 hours and 24 hours to seven days, respectively), though the statistical significance of this observation was not reported[14]. A study of PCS in 174 patients with mixed pathology found that over 70% of PCS occurs within the first week after cranioplasty[15], but another found no

such difference in incidence either side of a two-week cut off in 200 patients[16]. Further studies are required to fully understand the distribution of seizure timing after cranioplasty. Standardised definitions of 'early' and 'late onset seizures will help meaningful data comparison.

Use of anti-seizures medication

None of the included studies evaluated the efficacy of anti-seizures medications in preventing PCS. In most studies, it was not reported whether patients were routinely given prophylaxis. Recent evidence in cohorts with mixed pathology suggests that prophylactic levetiracetam can significantly reduce the incidence of PCS[16]. Whether this applies for TBI remains to be elucidated.

Limitations

This systematic review is limited by (i) the paucity of studies evaluating PCS following TBI, and (ii) an even more limited number of studies exploring risk factors of PCS. Included studies represent patients from wide-ranging locations, namely Australia[23], India[27], China[14; 24; 25], Missouri[18] and the UK[26], in addition to one paper reporting on a military cohort from the US army[4]. Varying treatment practices and mechanisms of trauma may affect generalisability of our findings. Furthermore, level of evidence is uniformly low. Only one study was of prospective design, but had a small sample size and follow-up for only one month post-cranioplasty[27]. Other studies demonstrate that this interval is insufficient for detecting the total incidence of PCS[23]. This prevents the differentiation between seizures as an isolated event following cranioplasty and a new diagnosis of epilepsy in included studies.

Conclusions and future research

Our review is the first of its type in the literature to systematically appraise the literature and identify risk factors of PCS in TBI patients. We herein report increasing age, contusion at the cranioplasty site, use of monopolar diathermy and use of autologous fascia at duraplasty as potentially significant risk factors. Further large, prospective cohort studies are required to evaluate (i) the true incidence of PCS; (ii)

whether delayed cranioplasty is truly predictive of PCS; and (iii) the validity of potential risk factors identified thus far. Finally, randomised controlled trials are required to assess whether prophylactic administration of antiepileptics is beneficial in reducing the risk of PCS in TBI patients.

Ethical Approval

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines. All co-authors have seen and approved this version of the submission and will see and prove the final version for publication if necessary.

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