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Decompressive craniectomy for the treatment of high intracranial pressure in closed traumatic brain injury (Review)

Sahuquillo J, Dennis JA

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[Intervention Review]

Decompressive craniectomy for the treatment of high intracranial pressure in closed traumatic brain injury

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ABSTRACT

Background

High intracranial pressure (ICP) is the most frequent cause of death and disability after severe traumatic brain injury (TBI). It is usually treated with general maneuvers (normothermia, sedation, etc.) and a set of first-line therapeutic measures (moderate hypocapnia, mannitol, etc.). When these measures fail, second-line therapies are initiated, which include: barbiturates, hyperventilation, moderate hypothermia, or removal of a variable amount of skull bone (secondary decompressive craniectomy).

Objectives

To assess the effects of secondary decompressive craniectomy (DC) on outcomes of patients with severe TBI in whom conventional medical therapeutic measures have failed to control raised ICP.

Search methods

The most recent search was run on 8 December 2019. We searched the Cochrane Injuries Group's Specialised Register, CENTRAL (Cochrane Library), Ovid MEDLINE(R), Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid OLDMEDLINE(R), Embase Classic + Embase (OvidSP) and ISI Web of Science (SCI-EXPANDED & CPCI-S). We also searched trials registries and contacted experts.

Selection criteria

We included randomized studies assessing patients over the age of 12 months with severe TBI who either underwent DC to control ICP refractory to conventional medical treatments or received standard care.

Data collection and analysis

We selected potentially relevant studies from the search results, and obtained study reports. Two review authors independently extracted data from included studies and assessed risk of bias. We used a random-effects model for meta-analysis. We rated the quality of the evidence according to the GRADE approach.

Main results

We included three trials (590 participants). One single-site trial included 27 children; another multicenter trial (three countries) recruited 155 adults, the third trial was conducted in 24 countries, and recruited 408 adolescents and adults. Each study compared DC combined with standard care (this could include induced barbiturate coma or cooling of the brain, or both). All trials measured outcomes up to six months after injury; one also measured outcomes at 12 and 24 months (the latter data remain unpublished). All trials were at a high risk of

bias for the criterion of performance bias, as neither participants nor personnel could be blinded to these interventions. The pediatric trial was at a high risk of selection bias and stopped early; another trial was at risk of bias because of atypical inclusion criteria and a change to the primary outcome after it had started.

Mortality: pooled results for three studies provided moderate quality evidence that risk of death at six months was slightly reduced with DC (RR 0.66, 95% CI 0.43 to 1.01; 3 studies, 571 participants; I^2 = 38%; moderate-quality evidence), and one study also showed a clear reduction in risk of death at 12 months (RR 0.59, 95% CI 0.45 to 0.76; 1 study, 373 participants; high-quality evidence).

Neurological outcome: conscious of controversy around the traditional dichotomization of the Glasgow Outcome Scale (GOS) scale, we chose to present results in three ways, in order to contextualize factors relevant to clinical/patient decision-making.

First, we present results of death in combination with vegetative status, versus other outcomes. Two studies reported results at six months for 544 participants. One employed a lower ICP threshold than the other studies, and showed an increase in the risk of death/vegetative state for the DC group. The other study used a more conventional ICP threshold, and results favoured the DC group (15.7% absolute risk reduction (ARR) (95% CI 6% to 25%). The number needed to treat for one beneficial outcome (NNTB) (i.e. to avoid death or vegetative status) was seven. The pooled result for DC compared with standard care showed no clear benefit for either group (RR 0.99, 95% CI 0.46 to 2.13; 2 studies, 544 participants; I^2 = 86%; low-quality evidence). One study reported data for this outcome at 12 months, when the risk for death or vegetative state was clearly reduced by DC compared with medical treatment (RR 0.68, 95% CI 0.54 to 0.86; 1 study, 373 participants; high-quality evidence).

Second, we assessed the risk of an 'unfavorable outcome' evaluated on a non-traditional dichotomized GOS-Extended scale (GOS-E), that is, grouping the category 'upper severe disability' into the 'good outcome' grouping. Data were available for two studies (n = 571). Pooling indicated little difference between DC and standard care regarding the risk of an unfavorable outcome at six months following injury (RR 1.06, 95% CI 0.69 to 1.63; 544 participants); heterogeneity was high, with an I^2 value of 82%. One trial reported data at 12 months and indicated a clear benefit of DC (RR 0.81, 95% CI 0.69 to 0.95; 373 participants).

Third, we assessed the risk of an 'unfavorable outcome' using the (traditional) dichotomized GOS/GOS-E cutoff into 'favorable' versus 'unfavorable' results. There was little difference between DC and standard care at six months (RR 1.00, 95% CI 0.71 to 1.40; 3 studies, 571 participants; low-quality evidence), and heterogeneity was high (I^2 = 78%). At 12 months one trial suggested a similar finding (RR 0.95, 95% CI 0.83 to 1.09; 1 study, 373 participants; high-quality evidence).

With regard to ICP reduction, pooled results for two studies provided moderate quality evidence that DC was superior to standard care for reducing ICP within 48 hours (MD −4.66 mmHg, 95% CI −6.86 to −2.45; 2 studies, 182 participants; I^2 = 0%). Data from the third study were consistent with these, but could not be pooled.

Data on adverse events are difficult to interpret, as mortality and complications are high, and it can be difficult to distinguish between treatment-related adverse events and the natural evolution of the condition. In general, there was low-quality evidence that surgical patients experienced a higher risk of adverse events.

Authors' conclusions

Decompressive craniectomy holds promise of reduced mortality, but the effects of long-term neurological outcome remain controversial, and involve an examination of the priorities of participants and their families. Future research should focus on identifying clinical and neuroimaging characteristics to identify those patients who would survive with an acceptable quality of life; the best timing for DC; the most appropriate surgical techniques; and whether some synergistic treatments used with DC might improve patient outcomes.

P L A I N   L A N G U A G E   S U M M A R Y

Partial removal of skull (decompressive craniectomy) to lower treatment-resistant high pressure in the skull and brain after traumatic brain injury

Review question

This Cochrane Review investigated the effects of a surgical procedure, decompressive craniectomy (DC), on survival and neurological (functional) outcomes for people who have a traumatic brain injury (TBI) that does not penetrate the skull, and high pressure inside the skull that does not respond to medical treatment. In DC part of the skull is removed so the brain has room to expand, and pressure inside the skull can decrease. We compared DC to conventional medical treatments in patients over 12 months old.

Background

The skull is a rigid bone 'box' that protects the brain. Consequently, if an injury causes the brain to swell, this leads to an increase in pressure within the skull. This excess pressure is known as high intracranial pressure (ICP), and is a frequent cause of death and disability in brain-injured people. If ICP cannot be controlled using standard medical measures, then DC may be tried. DC is the surgical removal of a portion of the skull to relieve pressure on the brain. Clinicians are uncertain how effective it is, and do not agree on its role in treatment of TBI.

Search date

This evidence is current to December 2019.

Study characteristics

We identified three relevant trials. One included 27 children (under 18 years); another trial was conducted in multiple sites and recruited 155 adults; and the third was conducted in 24 countries and recruited 408 participants (adolescents and adults). Each compared DC plus standard medical care against standard medical care alone.

In trials, the results are more reliable if patients and medical staff are unaware of which treatment a patient receives. However, the treatment given was evident in these trials, as it is not possible to conceal this type of surgery. The reliability of the results from the trial on children might have been affected because of the methods used to decide which children had DC, and because the trial stopped early. Similarly, the results of another trial might have been affected because of the treatment point at which DC was performed, and because of changes in methods for measuring outcomes. The third trial fit all of our criteria, and was well-conducted.

Study funding sources

Funders of two studies included national research bodies and the third (and smallest) study reported no specific source of funding.

Key results

Mortality

There is moderate-quality evidence that DC reduces the risk of death slightly at six months compared to standard medical treatment (3 studies), and high-quality evidence that it reduces death at 12 months (1 study).

Function

We analyzed functional outcome in three ways, splitting it into good and bad recovery as follows.

1. Good outcome (including serious disability) versus death or vegetative state: at six months there was no clear benefit for DC (2 studies, low-quality evidence), but at 12 months there was a clear benefit of DC (1 study, high-quality evidence).

2. Good outcome (including moderate disability) versus death, vegetative state or serious disability: at six months there was no clear benefit for DC (2 studies), but at 12 months there was a clear benefit of DC (1 study).

3. Good outcome (including minor disability) versus death, vegetative state, serious or moderate disability: at six months (3 studies) and 12 months (1 study) there was no clear benefit for DC.

ICP

DC was superior to standard medical treatment for reducing high ICP within 48 hours (2 studies, moderate-quality evidence).

Adverse events

Adverse events affected more people who have DC, than those who had medical treatment alone (low-quality evidence). These adverse events included problems that occur later, when the skull fragment was surgically replaced.

Quality of the evidence

The quality of our evidence ranges from high to very low. Evidence for outcomes other than mortality was complicated by differences concerning when to perform DC, as the two largest studies used different criteria for this. The small study on children produced low-quality evidence that DC has some benefits; a larger study on children is now in progress, and will improve the quality of our evidence once its results are available.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Decompressive craniectomy compared to medical treatment only for the treatment of high intracranial pressure in closed traumatic brain injury

Decompressive craniectomy compared to medical treatment only for the treatment of high intracranial pressure in closed traumatic brain injury

Patient or population: patients > 12 months of age with a severe traumatic brain injury and in a coma (post-resuscitation GOS score ≤ 8 points) with raised, refractory ICP
Setting: acute care
Intervention: (secondary) decompressive craniectomy
Comparison: medical treatment only (could include barbiturates, hyperventilation, moderate hypothermia)

Outcomes	Anticipated absolute effects* (95% CI)		Difference	Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with medical treatment only	Risk with decompressive craniectomy					
Mortality at 6 months	39.8%	26.3% (17.1 to 40.2)	13.5% (22.7 fewer deaths to 0.4 more)	RR 0.66, 95% CI 0.43 to 1.01	571 (3 RCTs)	⊕⊕⊕⊖ MODERATE 1	**Pooled analysis of trials with different inclusion thresholds for ICP (only the Taylor and RESCUEICP studies strictly involve refractory high ICP)** In one small pediatric study (Taylor 2001), the reduction in ARR for death for the DC group was 19.8% (95% CI -15% to 48.5%) In adults, the RESCUEicp trial showed that DC achieved a 22.1% ARR (95% CI 13% to 31%). In the DECRA study (lower ICP threshold) there was no significant difference in the ARR.
Mortality at 12 months	52%	30.7% (23.4 to 39.5)	21.3% fewer deaths (28.6 fewer to 12.5 fewer)	RR 0.59 (0.45 to 0.76)	373 (1 RCT)	⊕⊕⊕⊕ HIGH	The ARR was 21.5% (95% CI 11.6% to 31%). The NNTB to avoid this outcome was 5.
'Unfavorable outcome' as per original Cochrane	67.6%	67.6% (48 to 94.6%)	0% fewer (19.6 fewer to 27 more)	RR 1.00, 95% CI 0.71 to 1.40	571 (3 RCTs)	⊕⊕⊖⊖ LOW 2	This analysis uses the conventional GOS/GOS-E cutoff for favorable outcome (good recovery and moderate dis-

protocol at 6 months							ability) vs unfavorable (death, vegetative state and severe disability).
'Unfavorable outcome' as per original Cochrane protocol - at 12 months	71.5%	67.9% (59.4 to 77.9%)	3.6% fewer (12.2 fewer to 6.4 more)	RR 0.95 (0.83 to 1.09)	373 (1 RCT)	⊕⊕⊕⊕ HIGH	See above.
Changes in ICP from randomization up to 48 h follow-up	The mean ICP (intracranial pressure) change from randomization to 48 h ranged from 19 mmHg to 22 mmHg	MD 4.66 mmHg lower (6.86 lower to 2.45 lower)	MD 4.66 lower (6.86 to 2.45 lower)	MD -4.66, 95% CI -6.86 to -2.45	182 (2 RCTs)	⊕⊕⊕⊖ MODERATE[3]	A large trial (RESCUEicp 2016) in which ICP was measured differently (preventing meta-analysis) still confirmed these results.
Adverse events assessed in various ways, up to 24 months	Rates of adverse events in 2 trials were higher in DC groups (16.3% and 37%) overall versus (9.2% and 17%) in standard care. Adverse events included intra- or extracranial secondary injuries (anemia, hypoxia, infection, hydrocephalus, delayed hematomas, etc). Cranioplasty that followed craniectomy also led to complications.				544 (2 RCTs)	⊕⊕⊖⊖ LOW[4]	Significant adverse events always influence both mortality and functional outcome - so this may be seen as a redundant outcome.

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

ARR = absolute risk reduction; CI: confidence interval; DC: decompressive craniectomy; GOS: Glasgow Outcome Scale; GOS-E: extended Glasgow Outcome Scale; ICP: intracranial pressure NNTB: number needed to treat for an additional beneficial outcome; RR: risk ratio

GRADE Working Group grades of evidence
High quality: we are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: we are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[1] We have downgraded one level for indirectness due to the difference in inclusion criteria for the DECRA study
[2] We have downgraded two levels, one for indirectness due to the difference in inclusion criteria for the DECRA study and one for inconsistency (I^2 = 78%)
[3] We have downgraded one level for indirectness due to difference in inclusion criteria for the DECRA study. We have not downgraded because of imprecision (total sample size) in this case as a larger trial in which ICP was measured differently reported very results which are consistent with these (RESCUEicp 2016).
[4] We have downgraded two levels: one for indirectness due to the difference in inclusion criteria for the DECRA study; one for inconsistency due to the proportions of adverse events in the two different trials that measured them (DECRA 2011; RESCUEicp 2016).

BACKGROUND

Clarification of terminology: in this review we use 'DC' to refer to both to secondary DC specifically, as regards the intervention which is most relevant to this review (DC undertaken to reduce ICP refractory to first-or second tier treatment) and to decompressive craniectomy as a whole (where an overview is appropriate). When we refer to prophylactic or primary DC as 'P-DC', we mean specifically DC performed without regard to ICP, which is excluded from our review.

Description of the condition

Traumatic brain injury (TBI) is defined as "the occurrence of injury to the head that is associated with symptoms or signs attributable to the injury such as decreased level of consciousness, amnesia, other neurological or neuropsychological abnormalities, skull fracture, intracranial lesions or death" (Thurman 1999). Based on the mechanism of injury, TBI is classified as either closed (non-penetrating) or penetrating injury. Regardless of its cause, TBI is a major health problem worldwide and its burden is greatest in low- and middle-income countries (LMICs) where 85% of the world's population lives (De Silva 2009). Since 2001, when the Afghanistan war began, multiple armed conflicts have afflicted the world. In 2019, this is still an ongoing epidemic that has changed the spectrum of TBI significantly. Motor-vehicle crashes and falls are the most frequent causes of TBI-related death in civilians, while blast-induced TBI is the most frequent in the military (Meaney 2014). Most victims of both civilian and military TBI are young adult males, and because of the long-term disabilities sustained by survivors, severe TBI is a continual challenge to health systems, and a burden on families and the community in terms of monetary cost, suffering, and disability (Fearnside 1997). This systematic review is focused on closed TBI only and, therefore, excludes all military injuries including blast injuries. While blast injuries are the most frequent in modern wars and they are categorized as closed TBIs, they have a very complex pathophysiology and a completely different epidemiology (Warden 2006), which is why they are not included in this review.

A survey conducted by the European Brain Injury Consortium identified that 52% of TBIs were motor-vehicle related (Murray 1999). However, the pattern of injury is significantly different in high-income countries compared to LMICs (De Silva 2009). The Glasgow Coma Scale (GCS), introduced in 1974, is the most widely-used system for grading head injuries (Teasdale 1974), and contributes to most trauma classification systems and scores, despite its known limitations (e.g. its failure to incorporate brainstem reflexes, and its reported skew toward the motor response) (Sternbach 2000). According to the GCS, severe TBIs are present in patients with non-surgical post-resuscitation scores below or equal to 8, or those with higher scores that deteriorate to 8 or less. Severe TBI is found in about 10% of all TBI patients admitted to hospitals (Foulkes 1991; Kraus 1996), and the number of patients with unfavorable outcomes after severe TBI remains very high, even in highly-specialized neurotrauma centers in both the USA and Europe. The IMPACT (International Mission for Prognosis And Clinical Trial design) database collected data from 9205 patients with moderate (18%) and severe (82%) TBI who were enrolled in one of three prospective observational studies, or eight randomized clinical trials (RCTs) conducted between 1984 and 1997 (Marmarou 2007). An analysis of this database showed that TBI mortality dropped significantly in the years analyzed;

however, at least 50% of those with severe TBI died, or had a non-functional neurological outcome, even though they were enrolled in clinical trials conducted in centers that specialized in the management of severe TBI (Marmarou 2007). Analysis of the CRASH trial (**c**orticosteroid **r**andomisation **a**fter **s**ignificant **h**ead injury) - a more recent international, multicenter trial investigating use of corticosteroids after head injury - showed that 21% more patients died following severe TBI in LMICs than in high-income countries (De Silva 2009).

Despite a much better understanding of the pathophysiology and neurochemical cascades triggered by mechanical trauma as well as technical advances in neuromonitoring, the outcomes for people with severe TBI seem to have reached a plateau. Drugs tested in clinical trials - that were promising in preclinical studies - yielded disappointing results when tested in multicenter RCTs (Maas 1999). This failure may reveal that experimental models do not have the ability to simulate human TBI accurately; selection of target populations is inaccurate; studies are underpowered and have low probabilities of detecting clinically relevant effects; or knowledge of the optimal therapeutic windows for the drugs is insufficient. Further reasons could be a lack of penetration of the neuroprotective drugs into the brain; insensitivity of the outcome scales currently available to discriminate the potential benefits of a new treatment; or the intrinsic heterogeneity of TBI. An additional hypothesis is that severe primary brain damage may be present in some patients and that such damage cannot be modified by any available treatments (Sahuquillo 2002a).

High intracranial pressure in severe TBI

High intracranial pressure (ICP) is usually defined as an ICP above 20 mmHg measured within the subdural, intraventricular or intraparenchymal compartments. In the early 1990s, this was considered to be the most frequent cause of death and disability after severe TBI (Marmarou 1991), and it remains a frequent cause of death and disability. Juul 2000, in a post-hoc analysis of data from the international multi-center trial of the N-methyl-D-aspartate antagonist Selfotel, showed that the most powerful predictor of neurological worsening was the presence of an ICP ≥ 20 mmHg.

The cause of high ICP is always an increase in the intracranial volume produced by an increase in brain water content (edema), cerebrospinal fluid, cerebral blood volume, and/or mass lesions (contusions, hematomas, etc.). The risk of being classified as having high ICP can vary greatly depending on the methodology used for assessment and the Marshall classification category in which the patient is included (Marshall 1992; Poca 1998). Studies have used different methods to summarize ICP, including: the time spent above a certain threshold; mean ICP; standardized area under the curve; percentage of time above a threshold; and the percentage of patients requiring second-tier therapeutic measures. Thus, the true incidence of high ICP is notoriously difficult to establish.

Traditionally, it was considered that approximately 50% of severe TBIs with abnormal computed tomography (CT) scans had high ICP (Narayan 1982; Marmarou 1991); however, this incidence has changed significantly since the publication of studies from the late 1990s onwards. In a multicenter study of dexanabinol, only 10% of patients had ICPs above 25 mmHg (Maas 2006), while in the Traumatic Coma Data Bank (TCDB) report published in 1991, 72% had ICPs above 20 mmHg (Marmarou 1991). A possible reason

for this large difference is that half of the participants in the dexanabinol study had diffuse brain injuries (type II) but only 24% of participants in the TCDB report were classified in this category (Marmarou 1991). This lower incidence of high ICP is consistent with the randomized DECRA study (**de**compressive **cra**niectomy in diffuse traumatic brain injury), which included only 155 of the 3478 patients screened for eligibility (4.5%), mostly due to the presence of cerebral mass lesions and successful control of ICP with first-tier therapies (DECRA 2011). The lower incidence of raised ICP was consistent with the frequency observed in other RCTs (Cooper 2018; Maas 2006). The reason for this could be that, at least in participating centers (usually centers highly specialized in the management of TBI) better resuscitation strategies, better and faster transport to referral centers, and much more aggressive treatments of the mass lesions have been implemented.

Management of high ICP

In most centers worldwide, the treatment of high ICP is based on the recommendations of the *Guidelines for the Management of Severe Traumatic Brain Injury* developed by the Brain Trauma Foundation (BTF). These guidelines are endorsed by most scientific societies worldwide, and have been translated into many languages, and disseminated and applied in the USA, Europe, South America, China, and Japan, thus defining the core principles for managing severe TBI. These guidelines have been updated periodically since the first version was published in 1996 (Bullock 1996); the latest (4th) version was published in 2016 (Brain Trauma Foundation 2016). More recently, consensus-based (Class III evidence) has been put forward for a new management algorithm, but feedback from the neurological intensive care unit community is lacking thus far (Hawryluk 2019).

The sequence of steps for treating high ICP recommended in the BTF guidelines was based on an algorithm published in the first (1996) and second (2000) versions that was withdrawn in the third (2007) version (Brain Trauma Foundation 2007). Because the terminology of first- and second-tier maneuvers that was used in the 1996 algorithm is familiar to clinicians, and firmly ingrained in TBI literature, we have used it in this review. In brief, when ICP is above 20 mmHg, a set of general maneuvers is recommended (head elevation, normothermia, volume resuscitation, sedation, etc.). If these general maneuvers fail, a set of 'first line' therapeutic measures is started. These measures include cerebrospinal fluid (CSF) drainage, moderate hypocapnia (reduced CO_2 in the blood, i.e. pCO_2 30 mmHg to 35 mmHg) and mannitol administration (Brain Trauma Foundation 2007). When first-level measures fail to control ICP, only a few therapeutic options (second-tier therapies) are available unless potentially evacuable mass lesions are detected in the CT scan. Suggested second-tier measures include high-dose barbiturates, intense hyperventilation (pCO_2 < 30 mmHg), increasing mean arterial blood pressure, mild or moderate hypothermia, and decompressive craniectomy (DC). Of these, only the use of barbiturates has reached a Level II recommendation (based on Class II evidence) to treat high ICP; other medical and surgical therapies have failed to do so (Brain Trauma Foundation 2007). Other second-line therapies are based on Class III evidence and, therefore, are considered to be Level III recommendations. However, despite being recommended by the BTF, there is no robust evidence to show that any of these therapeutic measures are effective in improving patient outcomes (Roberts 1998; Sydenham 2009).

Despite the recommendations of the BTF guidelines on the use of barbiturates, a Cochrane Review did not find evidence that the use of barbiturates improves the outcome in severe TBI (Roberts 2012). Although barbiturates may reduce ICP, the reduction is not associated with lower mortality or improved outcomes in survivors (Roberts 2012). Barbiturates lower blood pressure in one out of every four patients, and this hypotensive effect may offset the beneficial effect of lowering ICP (Roberts 2012). Because of this lack of effective therapeutic measures, alternatives to barbiturates, and in particular DC, have been reconsidered in the treatment of high ICP.

Description of the intervention

Decompressive craniectomy in the management of TBI

Although there is uncertainty about who was the first surgeon to perform DC, the first known written report on decompressive surgery was written by Annandale in 1894 (Annandale 1894). He stated that 20 years previously he had operated on a patient with symptoms of high ICP, and he also reported on other patients under his care who had palliative DC. A comprehensive historical review of the first patients to undergo DC was published in 1906 (Spiller 1906). Although almost all pioneers of neurosurgery had performed this surgical procedure in the last part of the 19th century, as a palliative measure in inoperable tumors, Kocher was the first neurosurgeon to propose DC in patients with clinical symptoms of elevated ICP (Kocher 1901). Later, in 1905, Cushing made a detailed report on subtemporal and suboccipital decompression procedures to relieve high ICP in patients with inoperable brain tumors (Cushing 1905).

Historically, removal of different parts and quantities of the skull, with or without opening the dura mater or augmentative duraplasty, has been performed in TBI. These procedures have been used mainly to manage patients with high ICP and as a primary procedure in the evacuation of intradural lesions when the surgeon felt that the brain was 'tight' and edematous (Britt 1978; Cooper 1976). These procedures allow the brain to expand and consequently facilitate the control of high ICP. Although surgical decompression has no proven effect on the primary brain injury (injuries to the brain inflicted directly by the traumatic insult), it could reduce damage caused by secondary lesions (delayed brain damage) such as brain herniation and high ICP.

As a consequence of the experience gathered in military conflicts, in which neurosurgeons used DC as a strategy of damage control in the battlefield, it has been also used in civilian penetrating (missile) brain injuries. Intracranial gunshot wound (GSW) injuries are common in some countries and have a dismal prognosis. The assassination attempt against congresswoman Gabrielle Giffords in the USA in 2011, involved a gunshot to the head which was managed with early DC, resulting in an unexpected good outcome. This brought this procedure to the attention of international media (Lin 2012). However, this present review, which is an update of a previous Cochrane Review (Sahuquillo 2006), focuses exclusively on closed TBI, and therefore excludes any study or report published in the field of civilian or military penetrating GSW injuries.

Types of surgical decompression

Decompressive craniectomy can be performed in two very different clinical scenarios:

- **Prophylactic decompression or primary-DC (P-DC)** is defined as any bone decompression performed in patients undergoing surgery for the evacuation of any intradural lesion (Sahuquillo 2006). The aim of P-DC is not to control high ICP but to prevent expected postsurgical increases in ICP. In these procedures the decision is taken by the surgeon and is usually based on the CT scan, or intraoperative surgical findings (brain swelling, a 'tight' brain, or difficulties in repositioning the bone flap), or both. Some authors have also proposed the use of P-DC as a therapeutic strategy in the management of some types of brain contusions (Qiu 2012), as a damage control procedure in patients with acute subdural hematomas, or for severe brain swelling in countries with low resources and limited availability of intensive care facilities (Rubiano 2009). All these procedures are considered for the purposes of this review as P-DC. Two RCTs are currently in progress to define the role of P-DC in severe TBI with evacuated mass lesions (ISRCTN87370545; Zhao 2016).

- **Secondary-DC (DC)** was defined in the first version of this review as a procedure performed on patients with continuous ICP monitoring to control high ICP that is refractory to first- or second-level medical treatment (Sahuquillo 2006). This therapeutic option is used in some centers after first- or second-line therapeutic measures have failed to control ICP over a predefined threshold. We have also included patients who underwent a first surgical procedure to evacuate a space-occupying lesion and who had later developed delayed massive unilateral or bilateral brain swelling in the category of DC , when the purpose of DC was to control delayed high ICP (Guerra 1999a).

Surgical technique

A wide variety of surgical procedures for performing decompressive surgery has been reported. These variations include small to massive amounts of bone removal, uni- or bilateral bone decompression, scarifying the dura mater to decrease its rigidity, opening the dura mater - or leaving it closed - and sectioning the falx, among others. Localization of bone removal can be unilateral, bilateral, bifrontal, or subtemporal, or it can be expanded to what has been called 'circumferential decompression' (Clark 1968; Guerra 1999a; Münch 2000; Ruf 2003). The closing of the dura mater is also highly variable and the type of grafts used to augment decompression can be autologous, synthetic or biological (Huang 2010).

How the intervention might work

Increased ICP is the most frequent cause of death and disability following severe TBI. When high ICP is not related to evacuable mass lesions - for example in patients with unilateral or bilateral diffuse brain swelling - medical treatment is frequently ineffective in controlling ICP. Despite newly developed medical treatment modalities and improved methods of neuromonitoring, the mortality and morbidity caused by brain swelling remains high. In the absence of an evacuable mass lesion, most patients will either die, or survive with a non-functional status. No therapeutic options (barbiturates, other pharmacological options, or hypothermia) have been shown to be effective in these situations. An alternative approach when ICP is not controlled, is to increase cranial volume by removing part of the skull and opening the dura mater (i.e. decompressive craniectomy, DC). In many neurotrauma centers this treatment option is currently used as a rescue therapy.

Decompressive surgery for refractory intracranial hypertension is directed toward improving cerebral perfusion, preventing ischemic damage, and avoiding mechanical compression of the brain (brain herniations). The rationale for decompressive surgery is based on the Monro-Kellie law (Wilson 2016). According to this theory, intracranial volume should remain constant and volumetric compensations should be achieved by shifts in CSF, cerebral blood volume, or brain herniations. Removing a variable amount of bone, with or without leaving the dura mater open or augmented by a duraplasty, is a fast and effective means of increasing intracranial volume; reducing elevated ICP and increasing the intracranial space. In the Aarabi 2006 study, mean ICP decreased from 24 mmHg to 14.6 mmHg after decompression.

DC has been used since the beginning of neurosurgery, as a palliative treatment to relieve high ICP in people with inoperable brain tumors, hydrocephalus, or head injuries. The rationale for DC is that by removing a variable amount of bone, the skull is converted from "a closed box with a finite volume into an open one" (Cooper 1980). The benefits of DC in TBI are to facilitate the control of ICP, improve cerebral perfusion pressure, and avoid brain herniation and brainstem compression (Cooper 1980). Experimental models in the late 1960s and early 1970s showed that decompressive surgery was highly effective in reducing mortality in unilateral brain swelling. However, Moody and colleagues commented that, although unilateral hemicraniectomy significantly improved mortality in dogs with unilateral brain swelling, their "quality of survival has not been good" (Moody 1968). This and other negative reports introduced an important bias against this technique, supported by the influential clinical report of Clark 1968, in which these authors stated, "The reason for reporting this experience is to warn others from doing similar surgery". DC was almost abandoned in TBI due to early views that this surgery was ineffective and had too many complications with only a limited benefit (Cooper 1976; Cooper 1979; Cooper 1980). Improvements in surgical techniques, with greater possibilities of total or subtotal removal of brain tumors, and the introduction of hyperosmolar agents (urea, glycerol, and mannitol) and corticosteroids in the management of patients with high ICP reduced the need for this radical measure, which was discarded from the neurosurgical armamentarium by most neurosurgeons. Textbooks on TBI that were written in the 1950s, 1960s, and 1970s did not recommend this procedure.

Since the early 2000s, in addition to improvements in the prehospital care of patients with TBI, the use of well-designed protocols and the monitoring of ICP have changed the environment in which these patients are treated. Furthermore, both clinical and experimental studies have shown that DC significantly reduces post-traumatic intracranial hypertension and improves ICP dynamics, brain oxygenation, and brain metabolism in patients with refractory, high ICP (Ho 2008; Olivecrona 2007; Whitfield 2001a; Whitfield 2001b). In addition, findings from case reports, retrospective series, prospective non-randomized trials, and controlled trials with historical controls suggest that a favorable outcome might be expected in patients who are managed with targeted protocol therapies and given timely treatment with optimal surgical techniques.

Why it is important to do this review

This is an update of a previously published Cochrane Review (Sahuquillo 2008). Updating is important now because, since the

early 2000s, neurosurgeons and intensivists have shown renewed interest in DC for the management of high ICP refractory to first- or second-level therapeutic measures. Patients have a dismal outcome if ICP is not controlled quickly. Furthermore, highly favorable patient outcomes have been reported after surgical decompression in a small series of retrospective cohort studies and prospective non-randomized studies (Aarabi 2006; Gouello 2014). However, due to the weak methodological design of these studies, these favorable outcomes do not prove the effectiveness of this dramatic therapy, and many neurosurgeons are still reluctant to use it. Skepticism about the benefits of this procedure is influenced by the notion shared by many neurosurgeons that, even if DC does reduce ICP, the functional outcome of the survivors is not improved. Additionally, DC has potential adverse effects such as increased brain edema, subdural collections, hydrocephalus, and brain infarctions.

Both clinical and experimental studies have shown an increase of brain edema when DC is performed. A common clinical observation is that the brain herniates rapidly through the bone defect, resulting in a tense skin flap (Cooper 1979). This study showed that the brains of dogs with an induced cryogenic lesion had a significant increase in brain edema in craniectomized animals compared with control animals despite lower ICP. Animals with a closed skull had a mean lesion volume of 0.27 ± 0.19 mL while craniectomized animals had a mean volume of 1.96 ± 0.19 mL (Cooper 1979). However, more recent experimental studies show that in experimental models of cortical impact injury - that is, a model that induces mainly brain contusions - animals treated with early DC had a lower contusion volume compared with controls, and that brain edema did not increase when DC was performed early after injury (Plesnila 2007). Therefore, whether DC enhances brain edema in experimental models is still undetermined, and these findings have never been confirmed in clinical trials.

Despite this skepticism, the number of detected but excluded studies conducted since the first publication of this review in 2006 increased from 61 to well over 100 in 2019. Until recently, no results were available from RCTs in adults to confirm or refute the effectiveness of DC, although some prospective, single-center, non-randomized studies had suggested that a favorable outcome might be expected in selected patients using secondary DC (Gaab 1990). The subsequent significant increase in the number of retrospective or prospective non-randomized studies available indicates that DC is being increasingly used, despite the lack of strong evidence to support for its use.

A previous version of this review closed with the words of Kjellberg and Prieto in their seminal paper, "We have presented our appraisal of the case material (bifrontal decompressive craniectomy), not so much as proof of its superiority over other methods, but rather as provocation for further critical appraisal of its use" (Kjellberg 1971). Now that most results from two long-anticipated randomized clinical trials (DECRA 2011 and RESCUEicp 2016) have been published, we hope to shed light on this issue.

OBJECTIVES

To assess the effects of secondary decompressive craniectomy (DC) on outcomes of patients with severe TBI in whom conventional medical therapeutic measures have failed to control raised ICP.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials (including cluster-randomized controlled trials) were eligible for inclusion.

Types of participants

We included people over the age of 12 months with a severe traumatic brain injury (TBI) with a post-resuscitation Glasgow Coma Scale (GCS) score below or equal to 8 points, with raised intracranial pressure (ICP) that was refractory to medical treatment (analgesia, sedation, muscular paralysis, hyperosmolar solutions, hyperventilation, barbiturates, etc.). Since cerebrospinal fluid (CSF) drainage was considered as a first-level therapeutic measure in the second version of the *Guidelines for the Management of Severe Head Injury* (Bullock 2000), we have considered this maneuver to be a conventional medical treatment.

As in the two previous versions of this review (Sahuquillo 2006; Sahuquillo 2008), we have included only studies that defined the lesion using a CT scan and monitored ICP (regardless of the method). Since age and GCS score are strong independent predictors of outcome in TBI, we planned to conduct a subgroup analysis of the efficacy of DC in patients aged 18 years and under, 19 to 59 years, and over 60 years. If the procedure was conducted in severe or moderate TBI, we also planned to conduct a stratified analysis based on moderate TBI (GCS score 9 to 12) or severe TBI (GCS score ≤ 8).

Types of interventions

Types of intervention

This systematic review concerns the effects of secondary DC (DC) only, which we define as bone decompression with the dura mater closed, scarified, left open, or opened and augmented by duraplasty. However, the importance of opening the rigid and inelastic dura mater in any decompressive procedure was clearly stated in 1905 by Cushing, who said: "mere removal of bone alone does not usually answer as a palliative measure, for, owing to the inelasticity of the dura, sufficient decompression will not ensue until this membrane has been freely incised or removed" (Cushing 1905). Nevertheless, we have included studies in this review that performed large bone decompression without opening the dura mater, albeit noting that the procedure is suboptimal.

We excluded all studies in which primary-DC (P-DC) was conducted.

Types of comparator

We considered patients who received any standard medical treatment (regardless of the level of intensity) as the control group. We defined standard medical treatment as non-surgical therapy used to control ICP (i.e. hyperosmolar solutions, sedation and paralysis, hyperventilation, barbiturates, and/or moderate hypothermia). We also considered cerebrospinal fluid drainage for lowering ICP as an eligible, non-surgical therapy.

Types of outcome measures

Primary outcomes

- **Neurological outcome at 6 or 12 months** evaluated with the dichotomized Glasgow Outcome Scale (GOS) (Jennett 1975 or subsequent versions) and categorized into 'good' or 'bad' outcomes. Patients with a good recovery or moderate disability were included in the good outcome group while those who were severely disabled, remained in a vegetative state, or died were included in the bad outcome group. The introduction in 1981 of the extended version of the GOS (GOS-E) changed the traditional 5-point scale to an 8-point scale (Jennett 1981). The main difference between the original and the extended scale is that the latter separates patients in the moderate and severe disability categories into two subcategories: 'upper' and 'lower' on the basis of a structured interview (Wilson 1998). We, the review authors, are aware that thinking regarding this 'traditional' dichotomy has changed, and that ongoing controversies regarding what should be considered a good or favorable outcome involve value judgements about the quality of life of the survivors. As a result of this, we decided to present outcome data in a variety of formats, to help to contextualize the choices that patients, families and clinicians need to face in the informed consent process for DC (see Appendix 1; Appendix 2)
- **Mortality:** we included one month mortality in our protocol to avoid problems in evaluation of medium-term outcomes in contemporary clinical trials in which loss to follow-up is common (Sahuquillo 2002b). If DC is effective, a significant reduction in short-term mortality can be expected. However, mortality at one month is rarely reported in clinical trials, so we reported longer-term data for this outcome as well.

Secondary outcomes

- Significant reduction of ICP within 48 hours of randomization (threshold for meaningful reduction defined as 5 mmHg)[a]
- Adverse events, including infections, complications, etc.

[a]We have changed the threshold for successful, clinically meaningful management of ICP from the 2002 protocol value of a 10 mmHg reduction (Sahuquillo 2002b), to 5 mmHg.

Search methods for identification of studies

In order to reduce publication and retrieval bias we did not restrict our search by language, date or publication status**.**

Electronic searches

The Cochrane Injuries Group Trials Search Co-ordinator searched the following:

- Cochrane Central Register of Controlled Trials (CENTRAL; 2019, Issue 11) (which contains the Cochrane Injuries Trials Register) in the Cochrane Library (searched 8 December 2019);
- Ovid MEDLINE(R), Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid OLDMEDLINE(R) (1946 to 8 December 2019);
- Embase Classic + Embase (OvidSP) (1947 to 8 December 2019);
- ISI Web of Science: Science Citation Index Expanded (SCI-EXPANDED) (1970 to 8 December 2019);
- ISI Web of Science: Conference Proceedings Citation Index-Science (CPCI-S) (1990 to 8 December 2019);

- Clinicaltrials.gov (www.clinicaltrials.gov) (accessed 8 December 2019);
- International Clinical Trials Registry Platform http://apps.who.int/trialsearch/ (accessed 8 December 2019).

For the first published version of the review, the author also searched the following in March 2008:

- Neurobase (an additional proprietary database owned by the Neurotraumatology Research Unit, containing approximately 50,000 records on neurocritical care)
- Trials Central (www.trialscentral.org);
- Current controlled trials (http://www.controlled-trials.com/);
- Clinical Practice Guidelines (www.guidelines.gov);
- Google Scholar (http://scholar.google.com).

After 2008, the authors decided that only the Google Scholar search was likely to be of benefit and it was searched again in July 2015. Search strategies are reported in Appendix 3 and Appendix 4. Since 2015, The Publish or Perish software (Harzing 2007), which uses Google Scholar as a data source for citation analysis, was used to find new papers that cited the relevant papers we have cited in the included and excluded lists of studies in this review. The MEDLINE search strategy was adapted as necessary for each of the other databases: the added study filter is a modified version of the Ovid MEDLINE Cochrane Highly Sensitive Search Strategy for identifying randomized trials (Lefebvre 2011); the search strategy study design terms, as used by the UK Cochrane Centre (Lefebvre 2011), were also added to the Embase Strategy. For this recent update it was decided not to search CINAHL as it has not contributed references previously that were useful to the review.

Searching other resources

Handsearching

In addition to checking the reference lists of eligible articles, the following books were handsearched by a co-author of a previous version of this review, Fuat Arkan:

- *Intracranial Pressure*, Volumes I (1972) to XII (2002);
- *Brain Edema,* proceedings of the Brain Edema international symposia from 1984 to 1999.

These proceedings include selected, peer-reviewed, short articles of both oral and poster presentations, usually presenting a great deal of information on studies that frequently have never been published in full. Previously, they were not indexed in MEDLINE, but now they are indexed as supplements of *Acta Neurochirurgica*, and so are no longer searched separately for this review.

Consultation with experts

In the previous versions of this review we contacted researchers known to be interested or involved in this type of procedure to identify any clinical trials that have not yet been published, or older trials that have never been published. To identify unpublished studies, we sent each expert a comprehensive list of all relevant articles along with the inclusion criteria for the review and asked whether they knew of any additional published or unpublished studies that might be relevant. We sent emails or letters, or both, to 20 experts in the field of TBI. We received eight responses from these 20 requests. For this new update, we contacted two

additional experts to review the list of included and excluded studies (see the 'Acknowledgements' section).

Data collection and analysis

Selection of studies

The review authors (JS, JD) examined titles, abstracts, and keywords of citations from electronic databases for eligibility. We obtained full texts of all relevant records and assessed them to see whether they met the predefined inclusion criteria. When in doubt, we requested advice from the editorial team of the Cochrane Injuries Group.

Data extraction and management

As defined in the protocol, we worked independently and we both extracted data on the following variables from each selected study:

- age;
- gender;
- GCS score on admission;
- type of lesion, defined by the CT scan (focal versus diffuse);
- summarized ICP data;
- time from injury to surgical decompression for those allocated to intervention;
- surgical procedure;
- results of surgical decompression on ICP control;
- mortality and morbidity assessed by the GOS.

We also extracted data on details related to study methods and conduct, sufficient to provide judgements to assess the risk of bias of the studies (Higgins 2011a).

Assessment of risk of bias in included studies

Risk of bias tool

Although Jadad's scale was used in the first version of this review, it was not used in this update because its use has been discouraged by Cochrane methodologists (Jadad 1996). Instead, we have used the Cochrane 'Risk of bias' tool (Higgins 2011a), which is incorporated into the latest version of Review Manager 5 (Review Manager 2014). This scale is a domain-based evaluation, developed by a working group of methodologists, editors, and review authors, in which critical assessments are made separately for six different domains (sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and 'other'). Naturally, because of the nature of the intervention in this review, clinicians could not be blinded to the type of treatment to which the patient was allocated; however the domain of blinding was 'split' in order that information on blinding of the outcome evaluator could be assessed separately.

Measures of treatment effect

We calculated unadjusted treatment effects using Cochrane Review Manager 5 (RevMan 5) software where possible (Review Manager 2014).

Binary outcome data

As planned in the protocol, we calculated risk ratios and 95% confidence intervals (CIs) for dichotomous outcomes. In this review, we have also added the absolute risk reduction (ARR) and the number needed to treat for an additional beneficial outcome (NNTB) (to avoid the outcome of interest).

Continuous outcome data

In the original protocol we made plans to analyze continuous data by dichotomizing ICP control, but we found that ICP control had been assessed by means of different and non-comparable methods in the three included studies (i.e. hourly ICP, different intracranial hypertension indexes, the percentage of time ICP was above a threshold, etc.). So for this version of the review we decided that analysis of ICP data would be summarized best in the form of means and standard deviations (SDs) (where available), with 95% CI.

Unit of analysis issues

No unit of analysis issues arose within this review. Should cluster RCTs be identified in future, we plan to follow guidance on statistical methods for cluster-randomized trials described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b). We will seek direct estimates of the effect from an analysis that accounts properly for the design; alternatively, we will extract or calculate effect estimates and their standard errors (SEs) as for a parallel group trial, and adjust the SEs to account for the clustering (providing we are able to obtain an intra-class correlation coefficient (ICC), which describes the relative variability in outcome within and between clusters (Donner 1980).

Dealing with missing data

Where necessary, we contacted investigators of included studies and asked them to supply any unreported data.

We have recorded missing outcome data and dropouts, or attrition, for each included study in the individual 'Risk of bias' tables. We imputed no data.

Assessment of heterogeneity

We planned a visual inspection of forest plots (to assess magnitude and direction of effect), as well as an assessment of clinical variation across studies by considering the distribution of obvious important patient characteristics among trials (e.g. age, severity of TBI), and trial design or conduct factors (blinding of outcome assessment, losses to follow-up, treatment type). We have discussed statistical heterogeneity where relevant in terms of computing I^2 (Higgins 2002), a quantity that describes, approximately, the proportion of variation in point estimates that is due to heterogeneity rather than sampling error.

Assessment of reporting biases

We made every attempt to identify original protocols for included studies and to compare them with reported outcomes.

Funnel plots are meaningless at present, as we have only three studies in the review. For the future, if the number of studies is sufficient (minimum of 10), we plan to draw funnel plots (estimating differences in treatment effects against their SE). Asymmetry in these plots might be due to publication bias, but might of course also be due to a true relationship between trial size and effect size, such as when larger trials have lower compliance, and compliance is positively related to effect size. Where such relationships are identified, we will examine clinical variation of the studies (Sterne 2011).

Data synthesis

Where we judged interventions and populations to be sufficiently similar, we synthesized results in a meta-analysis, employing a random-effects model.

For calculating ARR and NNTB we used the online calculator available at ebm-tools.knowledgetranslation.net/calculator/prospective. We planned, at protocol stage, that if GOS scores were not available, we would include in the category of a 'bad' outcome those participants who were dependent on others for activities of daily living, remained in a vegetative state, and who died. We continued to follow this plan, despite the presentation of data in one study with a less traditional dichotomization that involved grouping those with 'upper severe disability' into the category of 'good outcome' (RESCUEicp 2016).

In addition to the original good/bad outcome analysis we described in the original protocol, and because this is an arbitrary dichotomization that generates controversies, we have conducted a new analysis that includes death or vegetative state versus other outcomes. We believe that death and survival in a vegetative status are considered 'bad' outcomes, without generating controversy (Honeybul 2017). This way, the interpretation of the results is easier for clinicians, and stands apart from the controversy concerning the particular point at which the threshold should be placed on the extended GOS (GOS-E) to define a 'bad/unfavorable' or 'good/favorable' outcome. In opinion of many, the cut-off to define bad and good outcomes is an arbitrary threshold, the definition of which should be left to the patients and caregivers, and not to the health providers.

Subgroup analysis and investigation of heterogeneity

As defined in our protocol, the analysis was designed to include all age ranges. When possible, we planned to perform specific subanalyses for the following groups:

- pediatric participants, defined as those under the age of 18 years;
- participants aged between 19 to 59 years;
- participants over 60 years of age.

At present, separate data for pediatric participants within the RESCUEicp 2016 trial have not been published, but we intend to use them for a subgroup analysis in future.

Sensitivity analysis

We planned no sensitivity analysis at protocol stage but, in future, should there be a sufficient number of trials, we will assess the impact on results of:

- allocation concealment; and
- blinding of outcome assessor.

Summary of findings and assessment of the certainty of the evidence

Summary of findings and assessment of the certainty of the evidence

We used GRADEpro 2015 to present the main results of this review in a 'Summary of findings' table(s), as necessary; one table per comparison.

Two review authors judged the overall quality of the evidence for each outcome as 'high', 'moderate', 'low' or 'very low' according to the GRADE approach (Schünemann 2011). We considered the following factors.

1. Impact of risk of bias of individual trials.
2. Precision of pooled estimate.
3. Inconsistency or heterogeneity (clinical, methodological and statistical).
4. Indirectness of evidence.
5. Impact of publication bias on effect estimate.

R E S U L T S

Description of studies

Results of the search

For the first version of this review (Sahuquillo 2006), the combined search strategy identified approximately 421 published and unpublished studies. After a full-text review 102 papers were selected. Of these studies only one fulfilled the eligibility criteria (Taylor 2001).

Subsequent searches run up to 2019 identified a further 891 references (768 after duplicates were removed). 304 records were examined in full text. From these we identified five records relating to two trials that were eligible for inclusion (DECRA 2011; RESCUEicp 2016), and one record concerned an ongoing study eligible for inclusion in a future update (RANDECPED 2019). See Figure 1. We incorporated a further 117 records into an annotated bibliography (Table 1).

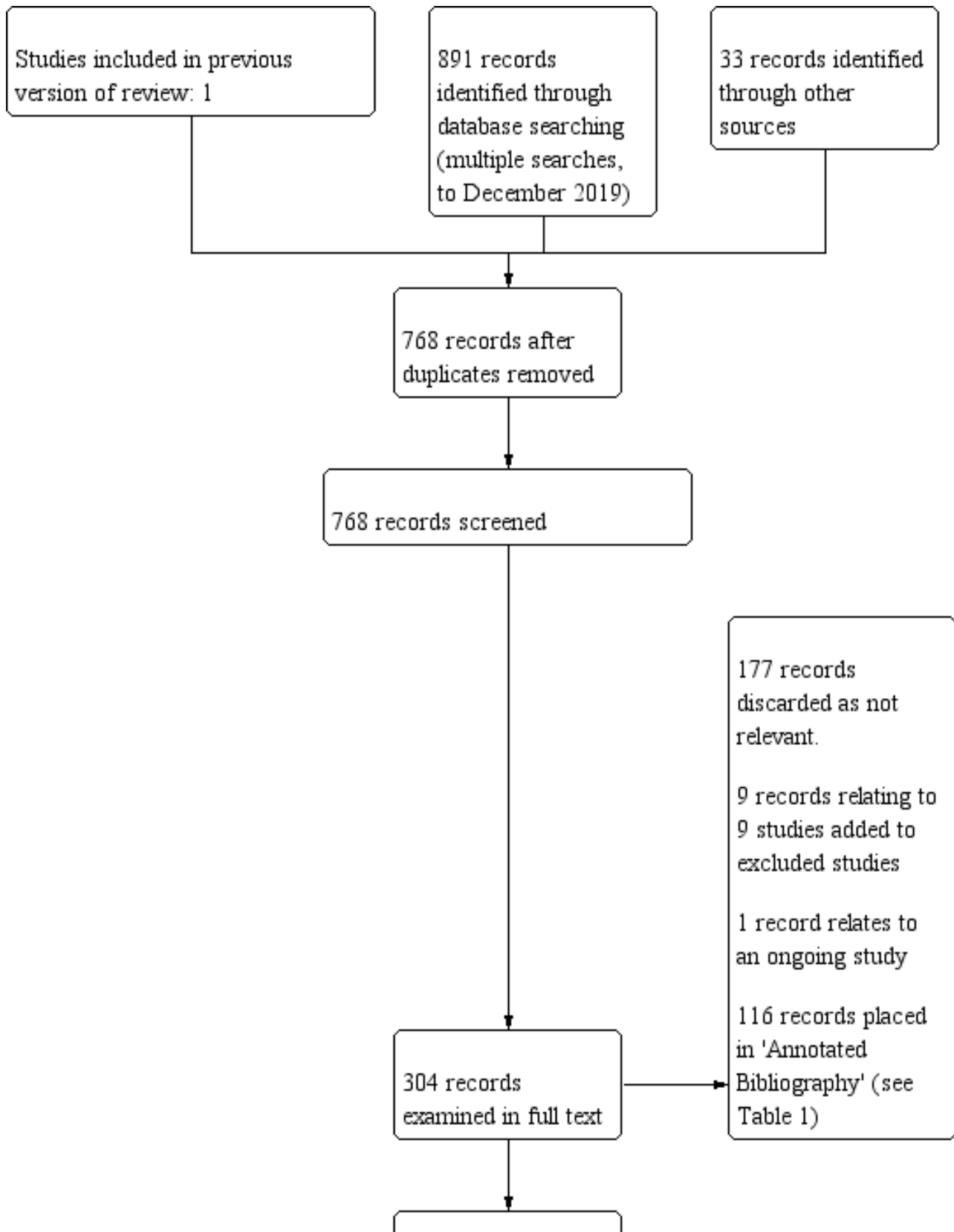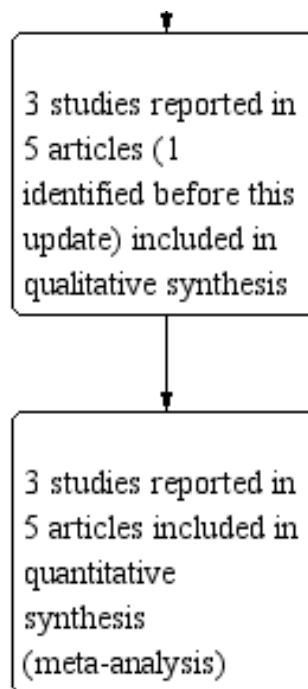## Figure 1. Study retrieval and selection process for current update

Figure 1.   (Continued)

Included studies

See also Characteristics of included studies.

Design

All three included studies were prospective, parallel randomized controlled trials (RCTs). Investigators from one single-centre trial randomized participants in blocks of four (Taylor 2001), and others, in a multisite trial, permuted blocks of random sizes and with stratification according to trial site (RESCUEicp 2016).

Sample sizes

Sample size at randomization varied from 27 participants in the Taylor 2001 study, to 155 in DECRA 2011, and 408 in the RESCUEicp 2016 trial.

The authors of the Taylor 2001 study, did not report conducting a sample size calculation, nor what the target for recruitment was. Recruitment ran for seven years between 1991 and 1998 before being halted; the trial was described as "stopping early" (Butt 2005; Taylor 2001). Authors attributed this decision to a reduction in the number of children being admitted to their intensive care unit (ICU) with severe TBI following the implementation of improved road safety measures and a lowering of highway speed limits in the area.

The DECRA 2011 study initially aimed to recruit 210 participants, then reduced this to 150. This trial was designed to identify an increase in the proportion of favorable outcomes (i.e. scores of 5 to 8 on the Extended Glasgow Outcome Scale [GOS-E] of 20% of participants undergoing DC, with a two-sided type I error of 0.05 and a power of 80%). With this power analysis, the original sample size calculated was 210 participants. However, at the interim analysis, the trialists redefined the primary outcome to detect a between-group difference of 1.5 in the median score on the 8-grade GOS-E and the sample size was recalculated to 150 participants

with a power of 80% and a two-sided type I error of 0.05. This decision was not without controversy, and may have caused the trial to have insufficient power to show any effectiveness of DC for improving favorable outcome according to a traditional approach.

Investigators within the RESCUEicp 2016 study calculated that a target sample of 400 participants would permit detection of a treatment effect of "15 percentage points between the two groups (difference in favorable-outcome rate of 45% vs. 60% ...) with 80% power at the 5% significance level (two-sided), allowing for a loss to follow-up of up to 15%" (Hutchinson 2016a).

Setting

Overall, evidence in this review was produced from trials undertaken in ICUs at hospitals in 25 countries. Recruitment was conducted between 1991 and 2014.

Data for individual studies were as follows:

- Taylor 2001 was conducted at a single site in Australia, with recruitment between 1991 and 1998;
- DECRA 2011 at sites in Australia, New Zealand and Saudi Arabia, recruiting between 2002 and 2010;
- RESCUEicp 2016 was conducted at 73 centres across 24 countries (Brazil, Canada, China, the Czech Republic, France, Germany, Greece, Hong Kong, Hungary, India, Ireland, Israel, Italy, Japan, Latvia, Malaysia, Peru, the Russian Federation, Saudi Arabia, Singapore, Spain, Turkey, the UK and the USA); recruitment ran between 2004 and 2014. Most participants in this trial (325) were recruited in the UK (291) or in continental Europe (34).

Participants

Age, gender and cause of injury

The Taylor 2001 study focused entirely on children (median age 120.9 months, range 13.6 to 176.4 months [one to 14 years of age]). The DECRA 2011 study enrolled participants aged 15 to 59 years (median age 23.7 years in the intervention group and 24.6 years in the control group). RESCUEicp 2016 included the oldest participants overall (mean age in the intervention group 32.3 years [SD 13.2], and in the control group 34.8 years [SD 13.7]).

Men made up 77% and 81% of participants in the DECRA 2011 and RESCUEicp 2016 studies, respectively. Taylor 2001 did not report the gender of participants or the cause of injury.

In the DECRA 2011 study, 85% of participants had suffered motor vehicle accidents, with the remaining injuries largely being related to bicycle or pedestrian accidents. The RESCUEicp 2016 study reported a more diverse range of injuries, i.e. motor vehicle accidents (35%); falls (32%), assaults (13%), pedestrian accidents (11%), and other/unknown (9%).

Severity at baseline

All studies shared the aim of controlling ICP before considering DC, and each referred to detailed protocols for stages or tiers of ICP-reducing treatment that preceded entry into the trial. All followed the recommendations given by the different versions of the Brain Trauma Foundation Guidelines (Bullock 1996; Brain Trauma Foundation 2007). In all cases, these treatments persisted for participants in the 'standard care' groups (variously described). ICP thresholds varied between studies and, in the case of Taylor 2001, across the course of the study itself.

The threshold at which DC was to be used varied across studies, which is a critically important aspect of their eligibility criteria, as it matters whether DC is used according to conventions applied worldwide - that is, only to treat ICP which has proved resistant to all conventional medical treatment (except barbiturates) - or if it has been used earlier in the treatment hierarchy, to treat moderate increases in ICP (Servadei 2011). We have summarized data on the variations below:

- Taylor 2001: the recommended threshold for ICP in pediatric patients was 20 mmHg according ; a figure maintained from early guidelines (Bullock 1996) to current ones (*Guidelines for the Acute Medical Management of Severe Traumatic Brain Injury in Infants, Children, and Adolescents,* updated in 2012 (Kochanek 2012). Cerebral perfusion pressure (CPP) targets are highly variable and age-dependent in the pediatric population, which is reflected in these guidelines (Bullock 1996; Kochanek 2012). Therefore, study investigators first established a threshold treatment aim of ICP ≤ 20 mmHg with an adequate CPP. This was defined initially as a CPP > 50 mmHg, but two years into the study in 1993 the "parameters for an adequate cerebral perfusion pressure were then adjusted for age (≥35 mmHg (1–4 years), ≥40 mmHg (5–8 years), ≥45 mmHg (9–12 years) and ≥50 mmHg (>12 years)". Later, in 1997, a "final definition for adequate cerebral perfusion pressure was then implemented ... [of] ≥50 mmHg (1–4 years), ≥60 mmHg (5–8 years) and ≥70 mmHg (>8 years)" (Taylor 2001). Children who had sustained ICP during the first 24 hours after admission, (ICP 20 mmHg to 24 mmHg for 30 minutes, 25 mmHg to 29 mmHg for 10 minutes,

30 mmHg or more for 1 minute) were randomized. Prior to paralysis, the median GCS of the DC group (n = 13) was 6 (range of 3 to 11); that of the medical treatment group (n = 14) was 5 (range 4 to 9). Investigators reported that the mean ICP, calculated from the last three prerandomization values, was 25.6 ± 8.1 mmHg in the control group and 26.4 ± 7.9 mmHg in the DC group.

- DECRA 2011: this study used the lowest ICP threshold of the three included studies. It set the treatment threshold for ICP as 20 mmHg for more than 15 minutes (continuously or intermittently) within a one-hour period. The median ICP during the 12 hours prior to randomization was 20 mmHg (interquartile range [IQR], 18 mmHg to 22 mmHg) in the sample as a whole. Concerns have been expressed about whether there is clinical equipoise to recruit patients to such an aggressive treatment at this threshold (Sahuquillo 2013). At baseline the median GCS for the DC group (n = 73) was 5 (IQR 3 to 7), and in the medical treatment group (n = 82) it was 6 (IQR 4 to 7).

- RESCUEicp 2016: the objective of this study was to maintain an ICP of < 25 mmHg, to be followed by randomization if this ICP was exceeded in any participant for a period of 1 to 12 hours. The ICP threshold used and the duration of raised ICP required for entry to the study was significantly higher than that used in the DECRA study. Therefore, the condition of participants at randomization was worse in this study. This study reported data by group and category of GCS scores; within the DC group, 53% had scores of 1 to 2 and 47% had scores of 3 to 6. Within the medical treatment group, 50% had scores at baseline of 1 to 2 and 50% had scores of 3 to 6.

Interventions and comparator groups

Intervention - definition of decompressive craniectomy amongst included studies

In Taylor 2001, those receiving DC underwent a bi-temporal craniectomy in addition to the standard care provided for the control group (defined as maximal medical treatment). DC involved removal of a 3 cm to 4 cm disc of temporal bone by extending the opening down to the floor of the middle cranial fossa. The dura mater was left intact and, in a few cases, scarified. According to our protocol, we consider this to be a suboptimal surgical procedure. Randomization took place a median of 16 hours after injury and in the intervention group, a "decompressive bitemporal craniectomy was performed at a median of 19.2 h (range 7.3–29.3 h) from the time of injury" (Taylor 2001). No child crossed over between treatment arms.

The DECRA 2011 study investigated secondary bifronto-temporo-parietal DC (without sagittal sinus and falx cerebri division) in adults with severe closed TBI in whom first-tier intensive care therapies did not control ICP as described above. The mean time from injury to randomization was 35.2 hours in the intervention group and 34.8 hours in the control group. The median time from randomization to surgery in the intervention group was 2.3 hours. Fifteen participants (18%) in the control group underwent delayed DC as a lifesaving intervention, according to the trial protocol (DECRA 2011).

In RESCUEicp 2016 the trial involved an initial standard protocol to manage participants with the objective of maintaining ICP < 20 mmHg. DC consisted of two options:

- for unilateral hemisphere swelling, a large unilateral fronto-temporo-parietal craniectomy; or,

- for bilateral diffuse hemisphere swelling, a large bilateral fronto-temporo-parietal craniectomy from the frontal sinus anteriorly to the coronal suture posteriorly and pterion laterally with a wide dural opening (pedicles based on the superior sagittal sinus medially) with the option of division of the falx anteriorly (Hutchinson 2006).

The RESCUEicp 2016 protocol required the allocated treatment to be implemented within six hours of randomization; the median time for 92% of those participants who underwent DC was 2.2 h. However, the protocol also permitted DC to be performed later at the clinician's discretion if the participant subsequently deteriorated (for example prolonged high ICP > 40 mmHg). This clause was required to cover situations in which the treating physician felt that withholding surgery would be against the best interest of the individual, and resulted in DC being performed in 37.2% of the control group (continued medical treatment).

Comparators

The comparator group in all three studies was medical management, variously described as 'maximal medical treatment', 'medical treatment', 'standard care' or 'continued medical management'. In Taylor 2001, this involved barbiturate-induced coma and moderate hypothermia; and in DECRA 2011, mild hypothermia, barbiturates, or both. In the RESCUEicp 2016 study there was a difference between the intervention and comparator groups' medical management, as the control group received high-dose barbiturates.

Outcomes

The original primary outcomes for this systematic review included neurological outcome at six or 12 months evaluated with the dichotomized GOS (Jennett 1975 or subsequent versions) categorized into 'good' or 'bad' outcomes (also known as 'favorable' and 'unfavorable'). We tried to evaluate ICP within 48 hours of randomization as a secondary outcome. In compliance with contemporary practice within Cochrane and as per GRADE, we also now include an outcome of 'adverse events' (Guyatt 2011).

Mortality

Mortality data were given in the Taylor 2001 study, but it required personal correspondence to establish the times at which deaths had occurred within the study, and in which groups (Butt 2005). DECRA 2011 reported on mortality in the hospital and at six months; and RESCUEicp 2016 reported at six, 12 and 24 months. The 24 month data for the RESCUEicp 2016 study and a planned subgroup analysis of data from younger participants have not been published yet.

Neurological outcome

All studies reported on neurological outcome, but with significant variations (see Appendix 1):

- Taylor 2001 reported this outcome on the GOS as 'favorable' or 'unfavorable' at six months after injury, using the traditional categories;
- DECRA 2011 initially planned to use the GOS-E in a similar way at six months, with 'unfavorable outcome' (i.e. a composite of death, vegetative state or severe disability) as the primary outcome. Following interim analysis, the primary outcome changed to become the score at six months. Outcome data at

12 months have been not published although the authors have presented them in an international meeting. We contacted the principal investigator to obtain these data and to include them in the analysis, but we were not able to obtain them;

- RESCUEicp 2016 also employed the GOS-E at 12 and 24 months (data from the 24-month time point have not yet been published). RESCUEicp 2016 also dichotomized results into 'favorable' and 'unfavorable', but the investigators changed the categories within the instrument to do so, saying, "conventionally, the GOS-E scale is dichotomized so that upper severe disability is categorized as being an unfavorable outcome, together with vegetative state and lower severe disability. Patients who are in the category of upper severe disability are largely independent around their homes but need assistance with traveling or shopping, whereas patients who are in the category of lower severe disability live in a supervised facility (care facility) or, if at home, need assistance most of the time. In view of the anticipated high proportion of poor outcomes in this trial population, it was agreed a priori by the trial team and the steering committee **that the upper-severe-disability category would be included in the definition of favorable outcome***" [emphasis added].

ICP control

ICP was recorded on an hourly basis in the Taylor 2001 study, and means and SEs were reported by group at 48 hours after randomization. ICP was recorded on an hourly basis in the early stages of the DECRA 2011 study, and group means and SEs were reported at 12 hours before and 36 hours after randomization. DECRA 2011 also reported the intracranial hypertension index (N of end-of-hour measures of ICP of > 20 mmHg/total N of measurements x 100).

The RESCUEicp 2016 study reported on ICP in multiple ways by group, prioritizing presentation of the comparative number of hours participants spent with ICP above 25 mmHg. Assessments included:

- ICP in the period after randomization;
- number of hours with ICP above 25 mmHg in the period after randomization;
- intracranial hypertension index 20 (number of end-of-hour measures of intracranial pressure of > 20 mmHg divided by the total number of measurements, multiplied by 100);
- intracranial hypertension index 25 (number of end-of-hour measures of intracranial pressure of > 25 mmHg divided by the total number of measurements, multiplied by 100); and
- cerebral hypoperfusion index (number of end-of-hour measures of cerebral perfusion pressure of < 60 mmHg divided by the total number of measurements, multiplied by 100) (Hutchinson 2006).

Adverse events

Assessment of adverse events within this type of study is difficult, as rates of mortality and complications are high in both groups, and it can be difficult to distinguish between true treatment-related adverse events and the natural evolution of the condition. Nevertheless, investigators in two of the three studies, DECRA 2011 and RESCUEicp 2016, specifically sought such data; the authors of the Taylor 2001 study did not report doing so.

Other outcomes

Trials differed in terms of other measures used, specifically:

- GCS score at discharge from the neurosciences hospital (RESCUEicp 2016);
- time in the ICU (DECRA 2011; RESCUEicp 2016);
- time to discharge from the hospital (DECRA 2011; RESCUEicp 2016);
- quality of life measured using:
  * the Health State Utility Index (HSU Index) [Torrance 1982]) in children at six months (Taylor 2001);
  * the 36-item Short-Form Health Survey in adults and the 10-item Short-Form Health Survey in children at 12 and 24 months (RESCUEicp 2016);
- proportion of survivors with score of 2 to 4 on GOS-E (DECRA 2011);
- economic evaluation (RESCUEicp 2016) (not yet published).

Sources of funding

The Taylor 2001 study did not report a source of funding. The DECRA 2011 study received funding from four research and/or public sector bodies in Australia and New Zealand; it was noted that funders had no role in the design of the study nor in data collection, analysis, interpretation or presentation. The RESCUEicp 2016 study was funded by a variety of UK-based public sector and charitable research bodies, which were also reported to have had no influence on the study design or analysis of results.

Excluded studies

Reasons for excluding nine clinical trials and over a hundred other manuscripts are exhaustively documented and appear in two tables: first, the table of Excluded studies and second, an annotated bibliography (Table 1). The latter is longer than that published in traditional Cochrane Reviews and is intended to indicate the widespread and increasing level of interest in this controversial field, and to pre-empt criticism that we have not scrutinized all available evidence.

Risk of bias in included studies

The risk of bias assessments for the three included studies are presented narratively below and with the Characteristics of included studies tables, as well as graphically in Figure 2. We assessed data as they were reported in publications relating to the DECRA 2011 and RESCUEicp 2016 studies, but for Taylor 2001 we also used personal correspondence (Butt 2005).

Figure 2. Risk of bias summary: review authors' judgments about each domain for each included study

Allocation

Sequence generation

We assessed the DECRA 2011 and RESCUEicp 2016 studies as being at low risk of bias for sequence generation. In the DECRA 2011 study, investigators used a stratified procedure and participants were randomized in blocks of two to four according to center and technique used to measure ICP; an automated telephone service was used to convey information to centers. In RESCUEicp 2016 a central telephone randomization service was used, and participants were allocated in permuted blocks of random sizes with stratification according to trial site.

We rated the remaining study, Taylor 2001, as being at a high risk of bias for this domain. This is because, after two allocations of four blocks of children to each arm, investigators apparently changed to using the Zelen method of randomization (Zelen 1979), which requires informed consent by parent or guardian after generation of sequence. (Furthermore, although randomization was as described

performed by blocks of four, the final numbers of participants were 13 and 14 in the two groups because the study was stopped after an interim analysis).

Allocation concealment

Two studies met the criteria for low risk of bias for this domain: in the DECRA 2011 study allocation was performed by independent researchers and conveyed by telephone, while in RESCUEicp 2016, concealment was assured because the service employed by the trialists did not release the randomization code until a participant had reached the third stage of the treatment protocol, at which point the decision to perform DC or not had been made (RESCUEicp 2016); furthermore, the sizes of the blocks used in the randomization were not revealed at time of allocation.

In the Taylor 2001 trial, the method of allocation concealment was initially concealed using sealed opaque envelopes, but we rated this trial as being at a high risk of bias because this method only applied to the first two blocks randomized (eight children), after

which Zelen randomization was used and allocation could not be concealed.

Blinding

Blinding of participants and personnel

Lack of concealment of treatment status is an intrinsic limitation of any decompressive study. We judged all three included studies to be at high risk of bias for blinding of participants or personnel.

Blinding of outcome assessors

Outcome assessors, were kept blind to treatment status in all three studies, leading to uniform assessments of 'low' for this domain.

Incomplete outcome data

We assessed the Taylor 2001 and RESCUEicp 2016 trials as being at low risk of bias for this domain. Investigators in the former planned to conduct analyses by intention-to-treat, but were not required to, as no participant crossed over to the other treatment group, and no participant who survived the first week was later lost to follow-up (Taylor 2001). In the RESCUEicp study, incomplete data were few and 93% (373/398) of the sample were evaluated at the 12-month follow-up. Missing outcome data were not imputed, but the investigators performed a sensitivity analysis for the primary-outcome measure in the per-protocol population (RESCUEicp 2016).

We assessed the risk of bias for the DECRA 2011 study as unclear for this domain. No participants were lost to follow-up; however, "fifteen patients (18%) in the control group underwent delayed decompressive craniectomy as a lifesaving intervention, according to the protocol" (DECRA 2011). In the standard care group in four of these participants, "craniectomy was performed less than 72 hours after admission, contrary to protocol". Investigators reported conducting all analyses "according to the intention to treat principle", which appears to be a robust strategy; however, the change in the primary outcome on the basis of interim analysis, combined with the fact that so many patients in the control group underwent DC make the usefulness of intention-to-treat analysis unclear.

Selective reporting

We judged the DECRA 2011 study to be at low risk of bias for selective reporting, despite the change in the primary outcome noted elsewhere. We were reassured by confirmation by the members of the trial's ethics/oversight committee that the trial conformed to its registered protocol (DECRA 2011). We judged the RESCUEicp 2016 study to be at low risk of bias, as the outcomes it reported matched those published in the trial protocol (Hutchinson 2006). The Taylor 2001 trial reported all expected outcomes, but as we did not have access to a protocol for this trial, we were compelled to assess it as being at an unclear risk of bias.

Other potential sources of bias

We considered two of the three included studies to be at unclear risk of bias for 'other' factors, specifically:

- stopping early (Taylor 2001);
- change in the primary outcome measure (DECRA 2011);
- baseline imbalance (DECRA 2011).

As a consequence, only the RESCUEicp 2016 study was rated as having a low risk of bias for this domain.

Specifically, Taylor 2001 trialists noted that the extended period of recruitment (seven years) meant that "A number of changes were made in our management of children with TBI during this trial, including changes to the definition of adequate cerebral perfusion pressure, less aggressive hyperventilation, and changes to hypothermia regimens and fluid management". Trialists also expressed the view that randomization in blocks of four may have reduced the effect of such changes (to medical management); so we cannot be sure there was no impact on results.

In DECRA 2011, the original primary outcome was the proportion of patients with an unfavorable outcome (i.e. a composite of death, vegetative state, or severe disability (a score of 1 to 4 on the GOS-E) assessed via a structured, validated telephone questionnaire six months after injury. However, after an interim analysis in 2007, this was changed to the functional outcome at six months after injury on the basis of proportional odds analysis. The change in the primary outcome - from the traditional GOS-E to the more complex and not-frequently used proportional odds analysis of the GOS-E - is unusual, and introduces a significant bias in the analysis of the final outcomes.

Baseline imbalances

In the Taylor 2001 study, both the control and the treatment groups were well balanced in important covariates such as age, GCS score at randomization, pupillary reactivity and ICP at baseline. In the DECRA 2011 study, randomization did not achieve balanced groups for pupillary reactivity, one of the most significant covariates. Bilateral unreactive pupils were present at baseline in 27% of participants in the DC arm but in only 12% of the control group (DECRA 2011). In the RESCUEicp 2016 study, both groups were quite similar at randomization, except for history of drug and alcohol use.

Effects of interventions

See: **Summary of findings for the main comparison** Decompressive craniectomy compared to medical treatment only for the treatment of high intracranial pressure in closed traumatic brain injury

We have chosen to pool results, despite the controversial ICP threshold at which the DECRA 2011 study permitted randomization to start (20 mmHg for 15 minutes). Servadei 2011 argued that "most neurosurgeons and intensivists dealing with TBI will not consider decompressive craniectomy in patients who have an intracranial pressure of around 20 mm Hg for such a short time" (see also Hutchinson 2011a; Sahuquillo 2013; Simard 2011a; Timmons 2011). In addition, this study used a modified version of the decompressive procedure described by Polin 1997, and thus is heterogeneous in terms of surgical technique, as it is the only trial in which falx sectioning was not performed.

Comparison: Decompressive craniectomy versus medical management alone

Primary outcome: mortality (1 month, 6 months, 12 months)

See Analysis 1.1.

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Mortality at one month after injury

None of the included studies published data for this outcome. Nevertheless, through personal contact with an author we acquired information for one small study involving 27 children (Taylor 2001). From this supplementary information, we established that all of the children who died within the course of the study did so within the first week (Butt 2005; Taylor 2001). Decompressive craniectomy (DC) did not reduce the risk of death compared to medical treatment (RR 0.54, 95% CI 0.17 to 1.72; 1 study, 27 participants; Analysis 1.1).

Mortality at six months after injury

All included studies reported results for mortality at six months (DECRA 2011; RESCUEicp 2016; Taylor 2001). Pooled results for the three studies suggest that the risk of death at six months following injury was reduced by DC compared with medical treatment (RR 0.66, 95% CI 0.43 to 1.01; 3 studies, 571 participants; I^2 = 38%; moderate quality evidence; Analysis 1.1). Taken individually, the reduction in ARR for death for the DC group in the Taylor 2001 pediatric study remained unchanged (19.8%, 95% CI −15% to 48.5%) because as noted above, all the deaths in this study occurred early on. In adults, the RESCUEicp 2016 trial showed that DC achieved a 22.1% ARR (95% CI 13% to 31%). The DECRA 2011 study (lower ICP threshold) showed no difference in the ARR.

Mortality at 12 months after injury

Only the RESCUEicp 2016 study (n = 373) reported data for mortality at 12 months. The risk of death at this time point was clearly reduced by DC compared to medical treatment (RR 0.59, 95% CI 0.45 to 0.76; 1 study; 373 participants; high quality evidence; Analysis 1.1) The ARR was 21.5% (95% CI 11.6% to 31%). The NNTB to avoid one death was five.

Primary outcome: neurological outcome (presented in three ways, at 6 months and 12 months)

See Analysis 1.2, Analysis 1.3, and Analysis 1.4.

Conscious of controversy around the dichotomization of the GOS scale, we have chosen to present results of the GOS/GOS-E scales in three ways, in order to contextualize the factors relevant to clinical/patient decision-making (see Appendix 1, and Appendix 2, for clarification). Following on from mortality, above, we first present results of death in combination with vegetative status, versus other outcomes.

Death/vegetative status versus other outcomes

Six-month follow-up

Two of the included studies reported results at six months for 544 participants (DECRA 2011; RESCUEicp 2016). We could not obtain data for the Taylor 2001 study. In the DECRA study (which had the lowest ICP threshold) there was an increase in the ARR of death/vegetative state for this combined outcome with DC. However, in the RESCUEicp 2016 study, there was a 15.7% ARR (95% CI 6% to 25%) with DC, and the NNTB to avoid the combination of death and vegetative status was seven participants. The pooled result for the two studies showed no clear difference between DC compared with medical treatment (RR 0.99, 95% CI 0.46 to 2.13; 2 studies, 544 participants; I^2 = 86%; Analysis 1.2).

Twelve-month follow-up

In the RESCUEicp 2016 study DC reduced the ARR for death or vegetative state at 12 months compared with medical treatment (RR 0.68, 95% CI 0.54 to 0.86; 1 study, 373 participants; Analysis 1.2).

'Unfavorable outcome', evaluated on a non-traditional dichotomized GOS-E

The DECRA 2011 and RESCUEicp 2016 studies (n = 571) reported results that could be pooled for this outcome, although it is non standard, and involves grouping the category 'upper severe disability' into the 'good outcome' division.

Six month follow-up

Pooled results indicated no clear difference between DC and medical treatment regarding the risk of an unfavorable outcome at six months following injury (RR 1.06, 95% CI 0.69 to 1.63; 2 studies, 544 participants; I^2 = 82%; Analysis 1.3); heterogeneity was very high, with an I^2 value of 82%.

Twelve-month follow-up

The RESCUEicp 2016 reported data at 12 months that showed a benefit of DC (RR 0.81, 95% CI 0.69 to 0.95; 1 study, 373 participants; Analysis 1.3).

'Unfavorable outcome', evaluated on the (traditional) dichotomized GOS (including GOS or GOS-E)

Six-month follow-up

All included studies (n = 571) reported results for this outcome (RESCUEicp 2016 presented results which allowed us to calculate necessary data). In the Taylor 2001 pediatric study, DC reduced the ARR for an unfavorable outcome by 39% (95% CI, 39% to 65%). The NNTB to avoid an unfavorable outcome (death, vegetative status and severe disability) was three children. In adults, the RESCUEicp 2016 trial showed that DC did not reduce the ARR of an unfavorable outcome compared with medical treatment.

In the DECRA 2011 study (with the lowest ICP threshold) the ARR for a bad outcome significantly increased in the DC group compared to standard treatment (ARR −19%, 95% CI −3% to −33%). However, this difference was in part justified by the imbalance between baseline characteristics of the control and treatment groups, which was remarked upon by the authors (DECRA 2011), and discussed elsewhere (Sahuquillo 2013).

Pooled results indicated no clinically significant difference between DC and medical treatment for the risk of an unfavorable outcome at six months following injury (RR 1.00, 95% CI 0.71 to 1.40; 3 studies, 571 participants; I^2 = 78%; Analysis 1.4); heterogeneity was very high, with an I^2 value of 78%.

Twelve-month follow up

The RESCUEicp 2016 study reported data that showed that DC caused a non-significant ARR in unfavorable outcome of 35% (95% CI −6% to −13%) at 12 months. The risk of an unfavorable outcome at this time point did not differ significantly between DC and medical treatment (RR 0.95, 95% CI 0.83 to 1.09; 1 study, 373 participants; Analysis 1.4).

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Secondary outcome: ICP reduction

The pooled results for the two studies that reported data in a format suitable for meta-analysis indicate that DC was superior to medical treatment in achieving this goal (5 mmHg reduction) within 48 hours (MD −4.66, 95% CI −6.86 to −2.45; 2 studies, 182 participants; I^2 = 0%; Analysis 1.5) (DECRA 2011; Taylor 2001). ICP data from the RESCUEicp 2016 study could not be pooled, as these were calculated in multiple ways, as described above. The results were consistent, however, with the findings of the meta-analysis, and showed a positive effect for both arms of the trial for the outcome of 'ICP control', manifestly in excess of the goal of a 5 mmHg reduction following intervention. The median ICP after randomization was reported as 14.5 mmHg (IQR 1.7 to 18.0) in the DC group and 17.1 mmHg (IQR 4.2 to 21.8) in the medical treatment group, with an absolute difference of −3.0 mmHg (IQR −4.1 to −1.8) . The P value for differences between groups was reported as < 0.001.

Secondary outcome: adverse events

Heterogeneity in reporting of adverse events prevented pooling for this outcome. Taylor 2001 did not report the collection of adverse events specifically. The DECRA 2011 and RESCUEicp 2016 studies provided explicit details of the nature and number of surgical and medical complications and adverse events throughout the trials in appendices to their main articles, and these data are reproduced within this review (Table 2). Authors of the RESCUEicp 2016 study summarized their extensive list, noting that "surgical patients ... had a higher rate of adverse events (16.3% vs. 9.2%, P = 0.03)" than participants within the medical treatment only group (Hutchinson 2016a). Authors of the DECRA 2011 study reported that a "total of 37% of patients in the craniectomy group and 17% of those in the standard-care group had one or more medical or surgical complications" and that the cranioplasty that followed craniectomy in the case of surviving participants (56 of 70) "also led to complications" (Cooper 2011).

DISCUSSION

Since this review was first published in 2006, the topic of decompressive craniectomy (DC) in patients with acute neurological injuries has changed significantly. There has been a major shift in the perception of the medical community of the role of DC in the management of acute brain injuries. For most surgeons and intensivists, DC was considered a 'primitive' and 'obsolete' surgical procedure for managing refractory increases in ICP. However, multiple retrospective and prospective - but non-randomized - clinical trials have shown that DC is effective in reducing the risk of death in traumatic brain injury (TBI) patients with high intracranial pressure (ICP), and in swelling-induced brain herniation in patients with large ischemic stroke or acute spontaneous intracerebral hemorrhages (Mitchell 2007; Moussa 2016; Rajwani 2017; Simard 2011b). Use of DC is increasing in many centers that manage acute brain injuries, possibly because of the documented use of DC by military neurosurgeons in war-related (penetrating or blast) head injuries (Ecker 2011). In addition, there is robust evidence obtained from multicenter RCTs that DC significantly reduces mortality and improves functional neurological outcome in patients with large middle cerebral artery ischemic stroke and brain edema at any age (Cruz-Flores 2012; Juttler 2007; Juttler 2014; Rajwani 2017).

Since this review was first published in 2006, the incidence of high ICP and how raised ICP is defined - and evaluated - have changed significantly in closed TBI due to many multicenter drug studies funded by the pharmaceutical industry. Analysis of these trials has raised two points: firstly, it highlights the different methods used to define 'high ICP', to evaluate its burden, and the effectiveness of different drug and non-drug therapies in controlling it; and secondly, that there has been a significant reduction in the number of patients diagnosed with increased ICP since the studies conducted in the 1990s.

Kahraman 2010 observed that "... despite the routine availability of vast amounts of data collected by automated monitoring systems, these crucial parameters (ICP and CPP [cerebral perfusion pressure]) are typically documented only intermittently and by hand, even in rapidly changing patients". The studies conducted thus far have used a wide variety of methods to record ICP data, thus introducing wide variability in the methodology used to present the data and to summarize it. So, while the true incidence of high ICP in severe TBI is notoriously difficult to establish, the effectiveness of different treatments to keep ICP under control is difficult to determine.

Recently, the 'dose of ICP' concept has been proposed and used as the best measure to summarize the burden of ICP (Güiza 2015; Kahraman 2010). The dose of ICP is defined as the area under the curve above the threshold of 20 mmHg by using high-resolution ICP recording - which can range from measuring every six seconds to minute-by-minute. This methodology allows the 'ICP dose' to be calculated and considers all intensity thresholds above 10 mmHg, not only the traditional 20 mmHg threshold (Güiza 2015). Use of this approach has shown that moderate ICP increases - between 15 mmHg and 20 mmHg - are, if sustained, related to unfavorable neurological outcomes (Güiza 2015). It has also shown that the critical ICP threshold for causing brain damage in TBI patients cannot be generalized and that this threshold is patient-dependent. The ICP cut-off at which the brain suffers secondary damage depends on the localization of the brain lesion and its characteristics (focal or diffuse lesion), the insult duration or 'dose', age, CPP and the autoregulatory status of the patient. Kahraman 2010 showed that 'pressure times dose' (PTD) expressed in mmHg/h is a much better measure of the burden of ICP than calculations of frequency or duration of episodes of high ICP, as the percentage of time with raised ICP is less predictive of the long-term functional outcome than the PTD. In addition, these authors observed that the disagreement between automated and manual data acquisition was very high and was not clinically acceptable (Kahraman 2010).

As a result of this relatively new information, and because we believe this variable was difficult to compare across the included studies, we changed the way outcomes attributable to raised ICP have been evaluated and reported in this updated review. In addition, most neurosurgeons and intensivists agree, that DC, when appropriately performed, significantly reduces ICP in most patients. A systematic review on the effect of DC on postoperative ICP showed that DC significantly decreases ICP and increases CPP in TBI patients with refractory high ICP (Bor-Seng-Shu 2012). However, the main disagreement - and lack of evidence - concerns whether this ICP reduction is translated to reduced mortality and to a better neurological outcome for the survivors. Therefore, the main focus of our systematic review was on evaluation of

neurological outcome and not the capacity of DC to reduce ICP, which we reported as a secondary outcome.

Summary of main results

In this updated review we found three eligible studies that included data from 590 participants. One small single-center RCT, Taylor 2001, was already included in the first version of this review (Sahuquillo 2006). In this 2019 update, we added two new studies, DECRA 2011 and RESCUEicp 2016.

Mortality

None of the three included studies published data for early mortality as defined in the protocol (30 ± 10 days after injury). We acquired information on this outcome for the Taylor 2001 study through personal contact, and learned that all the children who died during the course of the study did so within the first week (Butt 2005). The ARR at one month in children was 19.8%, but the wide confidence intervals (95% CI −15% to 48.5%) made this reduction in mortality in children treated with DC not statistically significant. In this study, the dura mater was not opened, which according to our predefined criteria made the surgical technique suboptimal. Despite the difficulties of running another, larger clinical trial on children, one has recently been registered (RANDECPED 2019); we await its findings with interest.

All included studies presented data for the outcome of mortality at six-month follow-up. The ARR for death was significantly reduced in participants who were treated with DC in the two studies that used the widely accepted ICP threshold of ≥ 25 mmHg (RESCUEicp 2016; Taylor 2001). In Taylor 2001, DC reduced the ARR for death by 19.8% (95% CI −15% to 48.5%). The RESCUEicp 2016 study, in which most participants were adults, showed an ARR for death of 22.1% (NNTB = 5) with DC. The DECRA 2011 study had a lower ICP threshold, and showed no statistically significant difference in the ARR between the intervention and the control groups. Pooled results for the three studies suggest that the risk of death at six months following injury was not reduced by DC compared with medical treatment (RR 0.66, 95% CI 0.43 to 1.01), but heterogeneity (I^2 = 38%) could be significant for this result. Only the RESCUEicp 2016 study reported mortality at 12 months; the ARR for death at this time point (21.5%) was significantly reduced by DC compared to medical treatment only (NNTB = 5).

All studies but DECRA 2011 showed a very significant reduction in mortality at any time point when DC was used to control refractory high ICP. The characteristics and caveats of the DECRA study (i.e. low ICP threshold to indicate DC, and suboptimal surgical technique) are summarized in this review and are discussed in detail elsewhere (Sahuquillo 2013). The DECRA 2011 study showed that when the trigger to define refractory ICP is set low - at 20 mmHg - DC is not superior to standard care in the management of patients with severe TBI.

Death or vegetative state versus other outcomes at six or 12 months

The evidence that DC improves six-month mortality in patients with ICP ≥ 25 mmHg is of high quality for adults and low quality for children. However, there are concerns that DC may prolong poor-quality life by increasing the number of survivors with major disability (Cruz-Flores 2012; Rajwani 2017). In our opinion, consideration of neurological outcome in any clinical trial involving

TBI patients requires a brief discussion of the long-established method used in most clinical trials to evaluate it. The Glasgow Outcome Scale (GOS) is a globally recognized scale for evaluating TBI outcome (Jennett 1975). It is the primary instrument used in most randomized controlled trials (RCTs) conducted in TBI since the results of the Traumatic Coma Data Bank were published in 1991 (Marshall 1991). The scale rates the patient's status into one of five categories: dead, vegetative state, severe disability, moderate disability, or good recovery. The lack of positive results in all phase III RCTs led some authors to question the sensitivity of the GOS to detect small but clinically relevant treatment effects (Weir 2012). This led to the recommendation of the extended GOS (GOS-E) as the optimal outcome scale by the IMPACT group (International Mission for Prognosis and Analysis of Clinical Trials in TBI) (Jennett 1981). The GOS-E scale splits three of the original categories, severe disability, moderate disability, and good recovery, each into lower and upper categories and thus extends the five original GOS categories into eight (Weir 2012). The IMPACT authors believed that the GOS-E yielded a clinically-relevant increase in statistical efficiency (Weir 2012). However, although the GOS-E increases the sensitivity of the original GOS, it also decreases the interobserver agreement and therefore, increases the risk of misclassification in untrained evaluators (Wilson 2007).

Traditionally, TBI trials have been analyzed by dichotomizing the GOS into categories: 'bad or unfavorable' outcome (death, vegetative state, or severe disability) and 'good or favorable' outcome (moderate disability or good recovery). Essentially, this was an arbitrary decision based on the tradition of considering any type of dependence for activities of daily living as a 'bad outcome'. In the RESCUEicp 2016 trial the trialists decided to group the categories differently, and included patients in the 'upper severe disability' category (who were capable of independence within the home) in the favorable outcome group (RESCUEicp 2016). However, the only justification for this new cutoff given to support this decision was that "it was agreed a priori by the trial team and the steering committee that the upper severe-disability category would be included in the definition of favorable outcome" (RESCUEicp 2016). Therefore, this was another arbitrary cutoff that introduced bias into the interpretation of the outcome results, especially as the highest level of interobserver disagreement identified when using the GOSE-E was for scoring this 'upper severe disability' category (Wilson 2007). Bearing all this in mind, together with caveats discussed later, we decided to use the conventional dichotomy and then added another option into our analysis, which was to group together death and vegetative state (i.e. outcomes conventionally considered negative by all involved in TBI care, versus all other outcomes, including severe disability, which may be acceptable to some patients, their families and even their clinicians). We feel this approach to interpreting outcome data in TBI trials is justified by the observation that any patient in a 'vegetative state' could never be regarded as experiencing a favorable outcome, even if the baseline prognosis is strongly adverse (Weir 2012). However, the use of the degree of dependency for activities of daily living to define an unfavorable or bad outcome, and who should define this - patients versus healthcare providers - is still a matter of debate.

We were able to extract this combined vegetative-death outcome at six months from two of the included studies (DECRA 2011; RESCUEicp 2016), but we could not obtain these data from the Taylor 2001 study. In the DECRA 2011 (with a lower ICP threshold) DC did not change the ARR for this combined outcome. However, in

RESCUEicp 2016 we found a significant 16% ARR (NNTB = 6). At 12 months, we could extract data to calculate this outcome only from RESCUEicp 2016; the results were nearly identical to those at the six-month time point.

Unconventional dichotomized neurological outcome

The DECRA 2011 and RESCUEicp 2016 studies reported results that could be pooled for this outcome, although it is non standard, and involves grouping the category 'upper severe disability' into the 'good outcome' division.Pooled results indicated no clear difference between DC and medical treatment regarding the risk of an unfavorable outcome at six months following injury, whilst heterogeneity was high as could be expected. At a year, the RESCUEicp 2016 reported reported a benefit of DC (RR 0.81, 95% CI 0.69 to 0.95).

Conventional dichotomized neurological outcome at six or 12 months

In this analysis we also used the conventional cutoff for favorable (good recovery and moderate disability) and unfavorable (death, vegetative state and severe disability) outcomes. All included studies reported results for this outcome at six months. In the Taylor 2001 pediatric study, DC significantly reduced the ARR for a bad outcome by 39% (NNTB = 3). In adults, the RESCUEicp 2016 trial showed that DC did not reduce the ARR of an unfavorable outcome when compared with medical treatment (RESCUEicp 2016). In the DECRA 2011 study the ARR for a bad outcome significantly increased in the DC group compared to standard treatment; this difference was partly due to the imbalance between characteristics of the groups at baseline (DECRA 2011; Sahuquillo 2013). Only the RESCUEicp 2016 study reported data at 12 months when the risk of an unfavorable outcome did not differ significantly between DC and medical treatment (RR 0.95, 95% CI 0.83 to 1.09; Analysis 1.4).

ICP reduction

Pooling of data from DECRA 2011 and Taylor 2001 showed DC was superior to medical treatment for achieving a 5 mmHg reduction in ICP within 48 hours (Analysis 1.5). ICP data from the third trial, RESCUEicp 2016, could not be pooled, but was consistent with these results.

Adverse events

The wide heterogeneity in reporting of adverse events prevented pooling for this outcome. The nature and number of adverse events throughout the trial are presented in Table 2. Although in general, patients treated surgically had a higher rate of adverse events, in the opinion of the review authors, the severity of these events was difficult to quantify and precluded the extraction of any relevant conclusion.

Overall completeness and applicability of evidence

We included three studies that sought to address the questions relevant to this review. With regard to ICP control, the results are quite convincing, and in line with most previous non-randomized clinical trials (Bor-Seng-Shu 2012), that showed ICP was significantly reduced after DC. With regard to mortality in children, although the results are clear regarding the ARR for death, the results were not statistically significant due to the small number of participants enrolled. As a result of this, we downgraded our judgement about the certainty of evidence to 'low ' according to

the GRADE guidelines for this population (Guyatt 2011). The full publication of the disaggregated results for children and young people from the RESCUEicp 2016 trial (currently, only preliminary data are available (Young 2017) and completion of the planned RANDECPED 2019 trial may improve certainty with regard to the pediatric population.

All three included studies managed severe TBI patients with high ICP according to some iteration of the BTF guidelines, so the treatments used are consistent with the management that patients receive in some high-income countries. However, the external validity of these findings is limited for low- and middle-income countries (LMICs) because the cornerstone of managing high ICP (according to all versions of the BTF guidelines) is ICP-monitoring, which is generally available only in high-income countries. Patients in LMICs have more than twice the odds of dying following severe TBI than those treated in high-income countries (OR 2.23, 95% CI 1.51 to 3.30) (De Silva 2009).

Despite this, it is clear that DC reduces mortality at all time-points and at any age when ICP is high and refractory to first-tier treatments (moderate or high quality evidence for adults). The results of the DECRA 2011 study should be interpreted with caution because of the high risk of bias of the study, the imbalance in the baseline characteristics of the participants, the suboptimal surgical procedure, and the low ICP threshold at which DC was indicated (Sahuquillo 2013). Our interpretation of the findings of this review are that when ICP is only moderately increased in adults, DC does not reduce either the risk of death or the risk of an unfavorable outcome.

Indeed, a major limitation of the current version of this review is that we cannot answer how and when to decide to conduct DC in patients without ICP monitoring. Therefore, clinicians reading this review should not draw any conclusions about whether the findings reported here can be extrapolated to patients managed without an implanted ICP probe. Indeed, these data cannot be integrated to any patient management protocol when surrogate measures of high ICP - such as the status of the basal cisterns or midline shift in the CT scan - are used. This is particularly relevant, because the usefulness of ICP monitoring in improving outcome has been questioned again after publication of the results from the BEST TRIP (Benchmark Evidence from South American Trials: Treatment of Intracranial Pressure) trial (Chesnut 2012). The results of this RCT reinforce the lack of evidence regarding efficacy of treatment that is based on ICP monitoring in patients with severe TBI highlighted by a recent Cochrane Review (Chesnut 2012; Forsyth 2015). According to this review - which was based on data from the BEST TRIP trial - there was no evidence of a difference in outcome between the strategy of continuously monitored ICP compared with care based on clinico-radiological assessment of raised ICP (Forsyth 2015). Although the results and interpretation of the BEST TRIP trial have raised ethical debates (Chesnut 2015; Sahuquillo 2014), and produced some new consensus statements recommending ICP monitoring in selected TBI patients, it is probable that the relatively high cost of ICP monitoring and the lack of evidence of its usefulness limits its implementation in LMICs in the foreseeable future. Therefore, the results and recommendations of this review are not applicable unless ICP is routinely monitored.

Quality of the evidence

We believe that despite all the bias described in Assessment of risk of bias in included studies, and the recognized heterogeneity of the three included studies in their designs and methodology, the evidence supports the conclusion that DC is not clearly superior to conventional treatment for mortality at six months (moderate quality evidence), but there is a clear beneficial effect on mortality at 12 months for adults with refractory high ICP (high quality evidence). Until detailed analyses of pediatric data are published, there is only low quality evidence for reduction in mortality for children according to the GRADE criteria (based on the data extracted from a single small study with some methodological flaws [Taylor 2001]). The main risks of bias in the Taylor 2001 study were: the method of patient allocation (Zelen's method); the lack of blinding of the investigators to the assigned arm; the length of time required to enroll the 27 patients included; the early termination of the trial; and the limited brain decompression achieved by the surgical technique used on these patients, in whom the dura mater was left closed or only scarified.

Zelen's approach has been considered by some scholars to be ethically questionable, while others find it perfectly acceptable (Hawkins 2004). Zelen's randomization method and consent process differ from conventional informed consent in two ways. First, participants are randomized to particular arms of a trial before anyone is asked for consent to participate. Second, only those patients randomized to the experimental arm are informed about the research and asked for consent (Hawkins 2004). Leaving aside ethical discussions, the method is feasible and can be accurate enough if the number of patients that refuse to participate is reported. In addition, an intention-to-treat analysis can also be performed with this design. The second issue in the Taylor 2001 study was the unblinding of the investigators to the assigned arm. We believe that this is an unavoidable limitation in a DC trial, since the investigators cannot be adequately blinded for obvious reasons. The CONSORT statement for non-pharmacological trials recognized and addressed this issue (Boutron 2008). In future, with this limitation in mind, every effort has to be made to mask the independent evaluators of the outcomes in these trials.Consequently, when evaluating the quality of these trials the emphasis should be shifted from the blinding of the investigators to appropriate blinding of the evaluators of outcome. A third issue in Taylor's trial was the time required to enrol the 27 included patients, which introduced bias due to the change in management of patients over the seven-year period. However, this would have affected both arms equally. The decision to stop the trial early was taken because of the results of an interim analysis, which showed - in the opinion of the investigators - clear efficacy of DC in reducing death and disability. This is scientifically reasonable and ethically sound when there is lack of clinical equipoise regarding any treatment. Finally, the brain decompression achieved in adults by bone decompression alone, as performed in this trial, we consider to be suboptimal in both adults and children. We categorized the evidence as low quality according to the GRADE guidelines because all of these shortcomings. The addition of complete data for children and young people from the RESCUEicp 2016 study and the planned RANDECPED 2019 trial, may improve the quality of evidence for DC in the pediatric population.

The DECRA 2011 was not a 'traditional' study of management of high ICP. In fact, one could argue that many clinicians were not in a state of clinical equipoise sufficient to require such a trial. The term clinical equipoise is defined as "…honest, professional disagreement among expert clinicians about the preferred treatment" (Freedman 1987). In other words, equipoise requires genuine uncertainty about the merits of the interventions studied. If two interventions are in equipoise, there is no good reason for believing that one is superior to the other (Chiong 2006). However, DECRA 2011 gives strong support for the avoidance of low ICP thresholds to indicate DC surgery in clinical practice (evidence of moderate quality), where it does not decrease mortality or improve long-term risk of unfavorable outcome compared with maximal medical therapy (DECRA 2011).

Potential biases in the review process

We are confident that our search strategy (Appendix 3) and study selection were robust. We have described the rationale for excluding studies in detail (Excluded studies). The fact that not all data from the RESCUEicp 2016 study have been released yet, limits our knowledge of outcomes at 24 months (Sahuquillo 2002b). The only results that may change significantly in future are those for the pediatric population. The Taylor 2001 study was a small study with important biases (Risk of bias in included studies). We do not know yet whether the inclusion of the unpublished data for the pediatric cohort of participants in the RESCUEicp 2016 and from the planned RANDECPED 2019 study will increase our confidence in the evidence for the pediatric population.

Agreements and disagreements with other studies or reviews

In the last few years although some narrative reviews have been published on this topic (Alvis-Miranda 2013; Eghwrudjakpor 2010; Young 2017), only a few systematic reviews have been published. Barthelemy 2016 was a review of DC in adults, and so excluded Taylor 2001, but included four RCTs (including DECRA 2011) in which more than 50% of the participants were under 18 years of age. We excluded three of the studies included in Barthelemy 2016 from this review because they investigated primary DC. The reasons for our exclusions are summarized in the Excluded studies section. Since we excluded three of the four studies that Barthelemy 2016 included, the conclusions of Barthelemy's systematic review cannot be compared with ours.

Grindlinger 2016 reported a single-center retrospective study of 31 patients with DC alongside a meta-analysis of all studies published in the 2006 to 2016 period. This meta-analysis included the DECRA 2011 study, together with nine non-randomized studies. The authors combined the results of these 10 studies to calculate the odds ratio for mortality and GOS-E categories of severe disability, vegetative status, or death. Grindlinger 2016 concluded that the outcome was significantly better when unilateral hemicraniectomy was conducted compared with bilateral DC. However, since the authors pooled all study types and did not control for the type of lesion at baseline (uni- or bilateral brain swelling), this conclusion is unreliable; the analysis is misleading and not comparable with our results.

Zhang 2017 was a systematic review and meta-analysis of the effects of DC in patients with high ICP. It included a total of 10 studies, with four RCTs in the meta-analysis. We excluded one of the RCTs from our review (Qiu 2009) (see Excluded studies), as it was designed to study the effectiveness of two different types of

primary unilateral decompressive procedures in adult patients with severe TBI, and unilateral brain swelling. The Zhang 2017 authors concluded that in this subgroup of patients, DC was effective in lowering ICP and reducing mortality, while its benefit on functional outcomes was not statistically significant.

Kolias 2018 was a narrative review that considered recent evidence in the field and concluded that: the DECRA 2011 trial showed that neuroprotective bifrontal DC for moderate intracranial hypertension is not helpful; however, the RESCUEicp 2016 demonstrated that last-tier DC for severe and refractory intracranial hypertension can significantly reduce the mortality rate, but is associated with a higher rate of disability. This review also discussed the role of primary DC when evacuating an acute subdural hematoma and the ISRCTN87370545 randomized trial. Other recent reviews (Garg 2019; Tsaousi 2018; Yue 2019) have come to similar conclusions as this review, albeit sometimes with differing criteria which are detailed in Table 1 (annotated bibliography).

Our review did not allow an in-depth consideration of the complications of DC and the required mandatory second surgery to repair the iatrogenic skull defect in survivors (cranioplasty or bone flap reposition). Early complications of DC have been recorded in most trials, but no trial has documented the complications related to bone replacement or cranioplasty in survivors. and different institutions perform cranioplasty at different times after DC. While the primary endpoint of all the included studies in this review was mortality at six months, problems can occur later. Early and late-surgical complications of DC can include: expansion of pre-existent hemorrhagic contusions; development of new ipsilateral or contralateral hematomas (subdural or intracerebral); seizures; cerebro-spinal fluid leaks; subdural hygroma or brain herniations through the craniectomy defect; post traumatic hydrocephalus; or a rare complication known as the syndrome of the trephined ('sinking skin flap syndrome') (Ashayeri 2016; Alvis-Miranda 2013; Kurland 2015). Kurland 2015 was a systematic review on the short- and medium-term intracranial complications of DC, that included data from randomized and non randomized studies. This review identified many DC-related complications of three major types: hemorrhagic, infectious/inflammatory, and disturbances of the CSF compartment. The review reported that the frequency of complications after DC was 13.4%. On average, 6.4% of the patients presented complications related to bone replacement or cranioplasty (Kurland 2015).

AUTHORS' CONCLUSIONS

Implications for practice

- In the pediatric population (patients under 18 years of age), there is very low quality evidence from one study that decompressive craniectomy (DC) reduces the risk of death and of an unfavorable outcome (death, vegetative status and severe disability) in children with intracranial pressure (ICP) refractory to medical treatment. This evidence is based on a single-center randomized trial that showed that DC - even without opening the dura mater - is effective in reducing ICP, mortality, and improving functional outcome (Taylor 2001). However, we (the review authors) consider that leaving the dura mater intact renders the procedure suboptimal both in adults and children. This study was very small and we judged it to have a high risk of bias for important domains, so its results must be interpreted

with caution. DC may be a reasonable treatment to include as a last step in children with high ICP refractory to all conventional medical options. We await publication of the pediatric results from the RESCUEicp 2016 trial and the planned RANDECPED 2019 trial to see whether the addition of new data improves the quality of evidence for DC in the pediatric population.

- In adults (18 years and above) with severe traumatic brain injury (TBI), and a lower level of refractory high ICP (> 20 mmHg threshold), DC does not reduce mortality or decrease the risk of an unfavorable outcome (moderate quality evidence). This conclusion is based on the results of the DECRA 2011 study, and should be interpreted with caution because of the high risk of bias of the study, the imbalance in the baseline characteristics of the participants and the suboptimal surgical procedure used. It is not possible to predict whether further studies with the same inclusion criteria that used a different surgical technique would change this conclusion. In addition, the lack of clinical equipoise to conduct new trials at this lower ICP threshold, makes it unlikely that the quality of evidence for this population will change.

- In adults with severe TBI and high ICP (≥ 25 mmHg) refractory to conventional medical treatment (based on the Brain Trauma Foundation guidelines (BTF)) DC has an effect in reducing mortality at six months (absolute risk reduction (ARR) 19.8%) and 12 months (ARR 21.5%) after injury. This evidence is high-quality and is based on the results of the RESCUEicp 2016 trial.

- In adults with severe TBI and high ICP (≥ 25 mmHg) refractory to conventional medical treatment DC-increased survival may occur at the expense of surviving with a more or less severe degree of disability, as DC does not decrease the risk of an unfavorable outcome measured in the traditional way of dichotomizing either the Glasgow Outcome Scale (GOS) or the Extended Glasgow Outcome Scale (GOS-E) into favorable or unfavorable outcomes (death, vegetative state and severe disability). This evidence is high quality and is based on the results of the RESCUEicp 2016 trial. The degree of disability that should be considered a 'bad outcome' is a matter of considerable debate, and is a variable that should be decided by patients and caregivers, and not necessarily by health professionals. It would be helpful to convey the information that DC improves the chance for survival, but with significant disability, to the patient's family or legal representatives before DC is conducted, so they have the information they need to participate in the medical decision process and take a decision that respects the patients' preferences, expectations and values.

- An unavoidable major limitation of this review is that we cannot provide evidence about how and when to decide to conduct DC in patients without ICP monitoring. Therefore, clinicians should not extrapolate the evidence provided here to patients managed without ICP monitoring. The relatively high cost of ICP monitoring, and the lack of robust evidence of its usefulness, will probably limit its implementation in low- and middle-income countries in the immediate future. Even in high-income centers, ICP monitoring is not conducted routinely in patients with severe TBI. The results of this review are not applicable outside those centers where ICP is routinely monitored.

Implications for research

New studies are needed - especially in the pediatric population - to refine the role of DC in the management of high ICP in patients for whom conventional measures have failed, and to increase

the level and quality of the available evidence. The difficulties in designing, implementing, and funding adequately powered randomized controlled trials (RCTs) are considerable; we therefore welcome news of a trial recently registered in France (RANDECPED 2019).

Given the effect of DC in reducing mortality in adults shown by the RESCUEicp 2016, new trials in adults should focus on identifying the clinical and neuroimaging characteristics which would be useful for identifying those patients who can survive with an acceptable quality of life. In addition, future RCTs should define the best timing for DC, the most appropriate surgical technique, and whether some synergistic treatments - hypothermia, barbiturates or any other 'neuroprotective' drugs - used together with DC improve the functional outcome and the quality of life of survivors. New studies should take into consideration the improved understanding of the pathophysiology of TBI, together with data obtained from multimodality neuromonitoring, and lessons that can be learned from previous clinical trials.

Selection of patients for surgery

DC clearly reduces mortality in patients with high ICP that is not controlled by any standard medical treatment. However, since survivors may live with a variable degree of severe disability, the selection of candidates with the potential for survival with a good functional outcome is crucial. In future trials, every effort should focus on avoiding performing DC in patients who combine high ICP with a devastating neurological injury (i.e. severe ischemic damage, severe forms of diffuse axonal injury, brainstem lesions, etc.). The conventional Marshall's classification - based on computed tomography (CT) scan - and the baseline neurological examination may be misleading and insufficient for this selection. The identification of new neuroradiological (magnetic resonance imaging-based) or non-neuroradiological characteristics (biomarkers) to map the degree of brain damage in TBI patients and the burden of primary injury may help healthcare professionals and families to make better decisions.

Propensity-score methods have been successfully applied in many clinical scenarios to reduce the likelihood of confounding when analyzing data from non-randomized studies. These are efficient methods for measuring the relationships between treatment and outcomes (Haukoos 2015). Application of these, or similar methodologies, to big databases, may help clinicians to fine-tune the selection process for identifying those patients where the extent and severity of irreversible brain damage will minimize the likelihood of them surviving with a good quality of life. This information may help clinicians to support family members involved in the decision-making process to decide on care that respects the patient's values and reduces the burden for the families and society, the goal being that "With a clear strategy and robust support, we can greatly increase the chances not only that the injured survive but that survivors have an opportunity to resume meaningful lives" (Brohi 2017).

Randomization method

Randomization is a problem in any surgical RCT in which patients cannot give informed consent, for which the outcome is generally bad, and the procedure is perceived as aggressive by the patient's family. Furthermore, the decision about inclusion in an RCT has to be taken early after injury, when the family is trying to cope with an abrupt and unexpected change in a person's health status. The ethics of Zelen's method of randomization and consent (in which consent is sought after randomization and only for those in the intervention group) need to be debated in this particular scenario (Homer 2002; Zelen 1979).

Medical treatment for high ICP

Medical treatment - also referred to as 'standard treatment', 'conventional treatment' or 'maximal medical therapy' - should be strictly defined, applied homogeneously in participating centers, and follow the best evidence available. This is difficult because of the wide variability among centers in deciding the thresholds or clinical criteria for refractory ICP. The concept of high ICP refractory to 'first' or to 'second' level treatments is widely used as a consequence of the algorithm of treatment introduced by the Brain Trauma Foundation (Brain Trauma Foundation 2000). However, there is wide heterogeneity in what these mean for different physicians, and whether hypothermia or barbiturates (or both) are included as standard.

It is important to know the intensity level of treatment a patient has received before randomization, so this information should be documented. The therapy intensity level index (TIL), designed to assess the intensity of ICP management on a 15-point scale, can be used to assess this (Maset 1987). A common source of bias in interpreting RCT results is that the different therapies used to control ICP are often used simultaneously in an additive or sequential manner, which blurs the individual effect of any therapy. Any further clinical trial on the effects of any therapy on ICP should include TIL as a measurement instrument.

Intracranial pressure (ICP) threshold for treatment

The ICP cutoffs used in the three studies included in this review are ambiguous and inconsistent. This is specially relevant in the pediatric population in which the thresholds change with the age of the patient as recommended by the pediatric guidelines (Kochanek 2012; Taylor 2001). None of the studies included in this review applied any measurement of treatment intensity. Currently the different duration of 'high ICP' between and within studies is very heterogeneous. Future multicenter trials need to reach a consensus on the most appropriate threshold at which to consider DC. This can be implemented by taking into consideration more reliable measurements of ICP when it is used as the only measurement, or combine ICP with the TIL in some composite score. The 'dose of ICP' concept is probably the best measure to use to summarize the burden of ICP (Güiza 2015; Kahraman 2010). Pilot studies would help to determine how future studies should define the ICP threshold using some type of composite score (ICP + TIL), or some critical 'dose' of high ICP, and not a traditional absolute value.

Surgical technique

The surgical procedures/techniques used for DC are very heterogeneous. Variations include: small to massive amounts of bone removal; uni- or bilateral bone decompression; opening the dura mater, scarifying it, or leaving it closed. The primary goal of decompression is restoration of cerebral perfusion by surgical enlargement of the intracranial space, and opening and augmenting the rigid dura mater. Studies in DC for ischemic malignant stroke have shown that enough bone must be removed to decrease ICP and to reduce the risk of venous infarctions associated with small bone openings, and the importance of opening the dura mater (Cushing 1905), and large duraplasty,

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has been recognized. Yoo 1999, evaluated the efficacy of bone decompression alone in a cohort of 22 patients who underwent bilateral DC to treat refractory high ICP after TBI or stroke. ICP was monitored before surgery, after bone decompression, and after opening the dura mater; the maximum ICP reduction was achieved after the dura mater was opened. In future surgical trials the extent of bone decompression, the limits of craniectomy, and the detailed surgical technique should be standardized and the volume increase obtained quantified by neuroimaging.

Synergistic neuroprotective therapies with decompressive craniectomy (DC)

As effective treatment of patients with severe TBI and high ICP reduces mortality, but can impose considerable long-lasting personal burdens on society and affected families, there is an urgent need to explore therapeutic strategies that may improve the number of patients with an acceptable functional outcome after DC. Whether additional neuroprotective strategies combined with DC may improve their outcomes deserves further study. Neuroprotective drugs or therapies - such as moderate hypothermia - added before, during, or after DC, may offer additional options for achieving a better outcome by extending the therapeutic window for DC or providing synergistic neuroprotection. In the scenario of malignant ischemic stroke, a recent pilot RCT has suggested that the combination of mild hypothermia and DC improves functional outcome when compared with DC alone (Els 2006). The DEcompressive surgery Plus hypoTHermia for Space-Occupying Stroke (DEPTH-SOS) trial, which investigated the safety and feasibility of moderate hypothermia for 72 hours in addition to early DC in patients with malignant middle cerebral artery infarction (Neugebauer 2013), provides a good example of a combined strategy. Synergistic therapies with distinct mechanisms of action may also be necessary in TBI patients to target different neurochemical cascades that play a role in the complex pathophysiology of patients with TBI and high ICP. Combined strategies may reduce the burden of primary lesions, and minimize the impact of secondary lesions, which will improve the functional outcome of survivors of DC.

Repositioning of bone flap

The bone flap removed during DC is replaced some variable time afterwards. The repositioning of the bone is not without risk to these fragile patients - in particular there is the potential for infection of the bone flap and subsequent complications (Kurland 2015). Historically, the consequences have not been well reported, but need to be closely monitored in future trials.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

DECRA 2011

Methods	**Design:** RCT (multicentre) **Title: De**compressive **cra**niectomy in diffuse traumatic brain injury (DECRA) **Setting:** acute settings in 15 tertiary care hospitals in 3 countries: Australia, New Zealand (88% of participants), and Saudi Arabia (12% of participants) **Recruitment period:** December 2002 to April 2010 **Maximum follow-up:** 6 months
Participants	**Inclusion criteria:** people 15 to 59 years of age who had early refractory elevation in ICP at a threshold of 20 mmHg. Refractory high ICP was defined as a "spontaneous (not stimulated) increase in intracranial pressure for more than 15 minutes (continuously or intermittently) within a 1-hour period, despite optimized first-tier interventions" (p 1494). **Exclusion criteria:** dilated and unreactive pupils; clinically relevant mass lesions; spinal cord injury; or cardiac arrest at the scene of the injury **N randomized:** 155 (intervention n = 73; control n = 82) **N completing 6-month follow-up:** 126 (intervention n = 59 ; control n = 67) **Age:** median age: intervention group = 23.7 years (IQR 19.4 to 29.6); control group = 24.6 years (IQR 18.5 to 34.9)
Interventions	**Intervention:** DC plus standard care. Standard care involved first-tier interventions following the recommendations of the Brain Trauma Foundation guidelines (Brain Trauma Foundation 2007), and included sedation, normocapnia and the use of mannitol, hypertonic saline, neuromuscular blockade and external ventricular drainage. Second-tier options for refractory elevation of ICP included mild hypothermia, barbiturates, or both. DC itself involved a "standardized surgical approach, modeled on the Polin technique ... This approach included a large bifrontotemporoparietal craniectomy with bilateral dural opening to maximize the reduction in intracranial pressure ... The sagittal sinus and falx cerebri were not divided. After craniectomy, the excised bone was stored at −70°C or in a subcutaneous abdominal pouch, according to the standard practice of the operating surgeon" (DECRA 2011, p 1494).

DECRA 2011 *(Continued)*

	Control: standard care alone
Outcomes	**Primary outcome**
	Functional outcome at 6 months on the basis of proportional odds analysis of the GOS-E (Jennett 1981)
	Secondary outcomes
	• ICP (measured hourly)
	• Intracranial hypertension index (N of end of hour measures of ICP of > 20 mmHg/total N of measurements x 100)
	• Proportion of survivors with score of 2 to 4 on GOS-E
	• Duration of time in ICU and in hospital
	• Mortality at 6 months
	Complications and adverse events were also measured for both surgical and medical treatments, including for cranioplasty in surviving craniectomy patients
Notes	The original primary outcome measure of this study (see also Cooper 2008) was "the proportion of patients with an unfavorable outcome, a composite of death, a vegetative state, or severe disability (a score of 1 to 4 on the Extended Glasgow Outcome Scale) as assessed with the use of a structured, validated telephone questionnaire at 6 months after injury .... After the interim analysis in January 2007, the primary outcome was revised to be the functional outcome at 6 months after injury on the basis of proportional odds analysis of the [GOS-E]..." (DECRA 2011, p 1495).
	Funders: "Funding was provided by the National Health and Medical Research Council of Australia; the Transport Accident Commission of Victoria, Australia; the Intensive Care Foundation of the Australian and New Zealand Intensive Care Society; and the Western Australian Institute for Medical Research .... funders had no role in the design of the trial protocol; in the collection, analysis, or interpretation of the trial data; or in the writing of the manuscript. The members of the executive committee attest that the trial was performed in accordance with the protocol, including revision of the primary outcome measure as described above, and vouch for the accuracy and completeness of the reported data" (Cooper 2011, p 1495).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote:** "Within the first 72 hours after injury, patients were randomly assigned to undergo decompressive craniectomy plus standard care or to receive standard care alone by using an automated telephone system. Randomization was stratified according to center and the method used to monitor intracranial pressure (external ventricular drain or intraparenchymal catheter) in blocks of two or four patients" (Cooper 2011, p 1494).
Allocation concealment (selection bias)	Low risk	Allocation was concealed - investigators were not aware to which group the participant would be assigned, and the allocation sequence was protected until assignment.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding was not possible for participants or personnel.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome measures were evaluated by telephone by 3 trained assessors who were unaware of the study-group assignments.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No participants were lost to follow-up; however, "fifteen patients (18%) in the control group underwent delayed decompressive craniectomy as a lifesaving intervention, according to the protocol" (p 1498). Of these, in four participants

DECRA 2011 (Continued)

| | | in the standard care group, "craniectomy was performed less than 72 hours after admission, contrary to protocol". Despite these issues, this trial has been assessed as having an unclear risk of bias because investigators reported conducting all analyses "according to the intention to treat principle" (p 1496).

We are obliged to remark that the change in the primary outcome on the basis of interim analysis and the fact that 18% of the participants in the control group underwent DC make the intent-to-treat analysis of unclear utility. |
|---|---|---|
| Selective reporting (reporting bias) | Low risk | This trial was preregistered (**Australian Clinical Trials Registry number:** ACTRN012605000009617)
Quote: "The members of the executive [ethics/oversight] committee attest that the trial was performed in accordance with the protocol, including revision of the primary outcome measure as described above, and vouch for the accuracy and completeness of the reported data" (p 1495). |
| Other bias | High risk | Randomization in DECRA did not achieve balanced groups for one of the most significant covariates, pupillary reactivity. Bilateral unreactive pupils were present at baseline in 27% of the participants in the DC arm but only in 12% of participants in the control group. In the Results section the authors stated that "After post hoc adjustment for pupil reactivity at baseline, the between group differences were no longer significant for the score on the Extended Glasgow Outcome Scale (adjusted odds ratio, 1.53; 95% CI, 0.86 to 2.73; P = 0.15) and for the risk of an unfavorable outcome (adjusted odds ratio, 1.90; 95% CI, 0.95 to 3.79; P = 0.07)" (p 1498).

In addition, the change of primary outcome is a cause for concern (see above). |

RESCUEicp 2016

| Methods | **Design:** RCT (multicentre)
Title: **R**andomized **e**valuation of **s**urgery with **c**raniectomy for **u**ncontrollable **e**levation of **i**ntra**c**ranial **p**ressure (RescueICP)

Setting: hospitals providing acute neuroscience care for severe TBI with neurosurgical services available 24 h/day, 7 days/week, in 73 centres within 24 countries (UK; 25 centres; Ireland: 1; Brazil: 2; Canada: 4; China: 2; Czech Republic: 4; France: 1; Germany: 4 Greece: 4; Hong Kong: 1; Hungary: 2; India: 1; Israel: 1; Italy: 3; Japan: 1 Latvia: 1; Malaysia: 2; Peru: 1; Russian Federation: 2; Saudi Arabia: 1; Singapore: 2; Spain: 3; Turkey: 2; USA: 3)

Recruitment period: January 2004 to March 2014
Maximum follow-up: 2 years |
|---|---|
| Participants | **Inclusion criteria:** participants aged 10 to 65 years with: a TBI with an abnormal CT brain scan; an ICP monitor in place, and raised ICP (defined as > 25 mmHg) for 1 to 12 hours, despite stage 1 and 2 measures (see below). Furthermore, "patients who had undergone an immediate operation for evacuation of an intracranial hematoma could be included as long as the operation was not a craniectomy (i.e., the bone flap was replaced at the end of procedure" (Hutchinson 2016a, p 2).

Exclusion criteria: having "bilateral fixed and dilated pupils, bleeding diathesis, or an injury that was deemed to be unsurvivable"

N randomized: total 408 (surgical intervention n = 206; medical treatment n = 202)
N used in analysis at 6-month follow-up: 398 (surgical intervention n = 202; medical treatment n = 196)

N used in analysis at 12-month follow-up: 373 (surgical intervention n = 194; medical treatment n = 179) |

Age: mean age: intervention group = 32.3 years (SD = 13.2); control group = 34.8 years (SD = 13.7)

Interventions	A standard protocol was used to manage participants with the objective of maintaining ICP < 25 mmHg by applying treatment in two stages, prior to allocation. Only if these stages were unsuccessful in controlling ICP, were the participants randomized to continuation of medical management versus DC.

Stage 1 measures included: sedation, analgesia, and head elevation with optional neuromuscular paralysis. If the ICP was not controlled, stage 2 options were deployed.

Stage 2 options included more advanced treatment measures such as: draining cerebrospinal fluid; administration of mannitol, hypertonic saline, or inotrope; moderate hyperventilation, moderate cooling (35°C-35 °C), loop diuretics, and steroids. In practice, investigators noted that Stage 2 could include "ventriculostomy (if an external ventricular drain had not already been inserted for ICP monitoring), pharmacologic blood-pressure augmentation, osmotherapy, moderate hypocapnia (PaCO2, 4.0 to 4.5 kPa [30 to 34 mmHg]), and therapeutic hypothermia" (Hutchinson 2016a, p 3). Barbiturates were **not** included as part of stage 2 measures but were reserved as part of continued medical treatment following randomization. This enabled direct comparison between the efficacy of DC and maximal medical treatment including the introduction of high-dose barbiturates.

If, despite stage 1 and 2 measures, ICP remained above 25 mmHg for 1 to 12 hours, then participants were randomized to either DC or continued medical treatment (stage 2) plus high-dose barbiturates. Allocated treatment was to be implemented within 6 hours of randomization. Decompressive surgery might be performed later at the clinician's discretion if the participant subsequently deteriorated (for example prolonged high ICP > 40 mmHg). This clause was required in case a situation arose in which the treating physician felt that withholding surgery would be against the best interests of the individual. The same principle applied to barbiturates in the DC group.

Outcomes	**Primary outcomes**

- GOS-E 6 months after randomization[a]

Secondary outcomes

- GOS-E results at 12 and 24 months after randomization[a]
- Mortality at 6, 12, and 24 months after randomization
- Quality of life at 6, 12, and 24 months after randomization (using the 36-item Short-Form Health Survey in adults and the 10-item Short-Form Health Survey in children);
- GCS score at discharge from the neurosciences hospital
- Assessment of ICP control including:
  * mean ICP in the period after randomization;
  * number of hours with the ICP above 25 mm Hg in the period after randomization;
  * intracranial hypertension index 20 (the number of end-hourly measures of ICP of >20 mm Hg divided by the total number of measurements, multiplied by 100);
  * intracranial hypertension index 25 (the number of end-hourly measures of ICP of >25 mm Hg divided by the total number of measurements, multiplied by 100);
  * cerebral hypoperfusion index (the number of end hourly measures of cerebral perfusion pressure of <60 mm Hg divided by the total number of measurements, multiplied by 100")
- Time in the ICU
- Time to discharge from the neurosciences hospital
- Economic evaluation
- Complications and serious adverse events

[a]As the investigators noted, this scale "conventionally ... is dichotomized so that upper severe disability is categorized as being an unfavorable outcome, together with vegetative state and lower severe disability. Patients who are in the category of upper severe disability are largely independent around their homes but need assistance with traveling or shopping, whereas patients who are in the category of lower severe disability live in a supervised facility (care facility) or, if at home, need assistance most of the time. In view of the anticipated high proportion of poor outcomes in this trial population, it was agreed a priori by the trial team and the steering committee **that the upper-severe-disability catego-**

RESCUEicp 2016 *(Continued)*

ry would be included in the definition of favorable outcome" [emphasis added] (Hutchinson 2016a, p 5).

Notes	We contacted the authors to obtain further details of the study (Hutchinson 2016b). We used some unpublished data that were supplied by the primary investigator (Mr PJ Hutchinson) to evaluate this study. **Funders:** the Academy of Medical Sciences (UK), The Health Foundation (UK), the MRC managed by NIHR on behalf of the MRC-NIHR partnership (UK) **ISRCTN identification**: ISRCTN66202560

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote:** "Patients underwent randomization, in a 1:1 ratio, with the use of permuted blocks of random sizes and with stratification according to trial site. To ensure concealment, the block sizes were not disclosed. Participants underwent randomization with the use of a central telephone randomization service" (Hutchinson 2016a, p 3).
Allocation concealment (selection bias)	Low risk	Concealment of group assignments was ensured, because the service did not release the randomization code until the participant had (despite stage 1 and 2 measures) maintained an ICP above 25 mmHg for 1 to 12 hours, after which assignment took place (stage 3).
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding was not possible for participants or personnel
Blinding of outcome assessment (detection bias) All outcomes	Low risk	For the primary outcome and the first secondary outcome (GOS-E at different time points), quote: "Two trial team investigators, who were unaware of the trial-group assignments, centrally adjudicated outcomes on the basis of the GOS-E questionnaires independently of each other according to a standardized approach. Disagreements were resolved by consensus between them or with the consultation of a third trial team investigator who was also unaware of the trial-group assignments" (RESCUEicp 2016, p 4)
Incomplete outcome data (attrition bias) All outcomes	Low risk	**Quote:** "Five patients were excluded from the analysis owing to withdrawal of consent, and 5 were excluded owing to a lack of valid informed consent, leaving 202 patients in the surgical group and 196 in the medical group. Of the 398 remaining patients, 389 were evaluated for the primary outcome (201 patients in the surgical group and 188 in the medical group), and 373 were evaluated at 12 months (194 in the surgical group, and 179 in the medical group)" (Hutchinson 2016a, p 5). The investigators therefore retained > 90% of sample in both arms. **Quote:** "Outcomes were reported in the intention-to treat population, which was modified to exclude patients who were lost to follow-up or who withdrew consent. Missing outcome data were not imputed. As prespecified in the statistical analysis plan, a sensitivity analysis was performed for the primary-outcome measure in the per-protocol population. The per-protocol population was defined as the patients in the intention-to-treat population who did not have a severe breach of protocol" (Hutchinson 2016a, p 4).
Selective reporting (reporting bias)	Low risk	The outcomes reported matched those published in the trial protocol (Hutchinson 2006).

Other bias	Low risk	No other sources of bias were detected.

Taylor 2001

Methods	**Design:** RCT (single centre)
	Setting: ICU in an urban hospital in Australia
	Recruitment period: November 1991 to December 1998
	Maximum follow-up: 11 months

Participants	**Inclusion criteria:** children aged between 12 months and 18 years who had sustained a TBI and had a functioning intraventricular catheter. Those who underwent ICP monitoring and had intracranial hypertension during the first day after admission (ICP 20 mmHg-24 mmHg for 30 min, 25 mmHg to 29 mmHg for 10 minutes, ≥ 30 mmHg for 1 minute) or showed evidence of herniation (dilatation of 1 pupil, or bradycardia) were eligible
	Exclusion criteria: none explicitly stated
	N randomized: 27 (DC intervention n = 13; medical treatment only n = 14)
	N used in analyses: 1 child died within 48 hours of allocation in the intervention group and 3 died in the medical treatment group during the same period (Taylor 2001). An investigator later confirmed that overall 3 children died in the DC group over the study period, and 6 in the medical treatment group, all within a week of the commencement of the study (Butt 2005). This left 11/13 and 10/14 surviving at 6- and 11-month follow-up. Data for 1 child were missing at 6 months, but present at 11 months.
	Age: median age: 120.9 months, range 13.6 months to 176.4 months (i.e. 1 to 14 years of age)

Interventions	**Intervention:** participants underwent a bi-temporal craniectomy (intended to take place within 6 h of randomization) in addition to maximal medical treatment. A 3 cm to 4 cm disc of temporal bone was removed by extending the opening down to the floor of the middle cranial fossa. "The dura was left intact and, in a few cases, scarified" (Taylor 2001, p 155).
	Controls: maximal medical treatment alone. The full standardized protocol for this treatment was published (Taylor 2001; Appendix A, pp 158-60). It included barbiturate-induced coma and moderate hypothermia (in all cases).

Outcomes	**Primary outcome**
	Functional assessment of outcome (using a 'modification' of the GOS [Jennett 1975] at 6 months). "Outcome categories for the modified GOS were defined as normal; functionally normal (both intellectually and physically) but requiring medication or medical supervision; mildly disabled but likely to lead an independent existence; moderately disabled and dependent on care; severely disabled and totally dependent on care (including children in a persistent vegetative state); and death. Children who were normal or functionally normal or had a mild disability were defined as having a favorable outcome; children who had a moderate or severe disability or had died were defined as having an unfavorable outcome. The nature of disability was classified as motor, cognitive or behavioural" (Taylor 2001, p 159). Data were obtained by telephone interviews with parents or guardians
	Secondary outcomes
	- Control of ICP in the immediate period
	- Quality of life measured at 6 months using the Health State Utility Index (HSU Index) (Torrance 1982)
	Mortality was also assessed but the time of deaths and the groups in which they took place were not clearly reported in the paper, but afterwards confirmed through personal correspondence (Butt 2005).

Notes	We contacted authors to obtain further details of the study. We used unpublished data that were supplied by the author (Dr W Butt) to evaluate this study. In addition to other issues identified below, Dr Butt informed us that the reason for the total number of randomized participants ending up as 13 and

Decompressive craniectomy for the treatment of high intracranial pressure in closed traumatic brain injury (Review)   **45**

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Taylor 2001 *(Continued)*

14, respectively, despite randomization performed by blocks of four, was that an interim analysis was performed and the study had been stopped early (Butt 2005).

Funders: none mentioned

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	In this trial the first 8 participants were randomized conventionally in blocks of 4, with the use of random numbers tables. Thereafter, the Zelen method was used, where consent followed randomization and participant preference was taken into account (Butt 2005).
Allocation concealment (selection bias)	High risk	Initially, serially marked and sealed opaque envelopes were used, but given that Zelen randomization was later adopted, allocation concealment must be regarded as compromised (Butt 2005; Taylor 2001)
Blinding of participants and personnel (performance bias) All outcomes	High risk	It was not possible to blind either participants or personnel to this intervention.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Evaluators of outcome were blinded to the allocated treatment (quote: "The outcome assessor was blinded to the treatments received whilst in ICU and there was a prescribed list of questions for consistency" (Butt 2005)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Analysis via intention to treat was planned, but in the event, there were no dropouts. 1 child allocated to the DC group could not be contacted for the 6-month follow-up but was successfully contacted at final follow-up at 11 months.
Selective reporting (reporting bias)	Unclear risk	All significant primary and secondary outcomes appear to have been reported, but in the absence of a published protocol, assessment for this domain must remain unclear.
Other bias	High risk	The study was stopped early because increases in road safety in the local environment meant that there were fewer eligible participants available. In addition, over the 7 years in which recruitment took place, changes were made to the medical treatment protocol.

Abbreviations

CT: computed tomography
DC: decompressive craniectomy
GCS: Glasgow Coma Scale
GOS: Glasgow Outcome Scale
GOS-E: extended Glasgow Outcome Scale
ICP: intracranial pressure
ICU: intensive care unit
RCT: randomized controlled trial
TBI: traumatic brain injury

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Bhat 2013	**RCT**. **Excluded due to ineligible comparator (DC not compared to usual care)**. This prospective RCT evaluated the efficacy of a new technique ('multi-dural stabs') to open the dura mater after

Study	Reason for exclusion
	wide DC in 119 cases compared with DC and the conventional dural opening (106 controls) to decompress severe acute subdural hematomas (> 25 mL volume and > 5 mm midline shift) in patients with severe TBI (GCS ≤ 8) and severe brain swelling. Patients were operated on within 6 hours of injury. The mortality of patients with the multi-dural stab technique was significantly lower (22.7%) than patients who underwent DC and the conventional dural opening (53.8%).
ISRCTN87370545	**Protocol for an RCT. Excluded (rather than placed in 'ongoing studies') due to overlapping (but ineligible) population and ineligible comparator.** Protocol for an RCT to test whether people with head injuries who undergo emergency brain surgery and have an acute subdural hematoma evacuated have better outcomes if the bone flap is left out (DC) or replaced before closing the skin.
Jiang 2005	**RCT. Excluded due to ineligible comparator.** This multicenter study was designed to compare the effectiveness of 2 different surgical techniques for performing surgical decompression, with no 'standard care' control. 486 patients with severe TBI and refractory high ICP were randomly assigned to undergo either unilateral standard trauma craniectomy or what was called 'limited' craniectomy. The standard DC involved a 12 cm x 15 cm craniectomy with dura mater opened and duraplasty performed with temporal fascia. The limited procedure was the same except that the bone removal was smaller (6 cm x 8 cm). An important bias in this study was that DC was conducted together with hematoma evacuation and/or contusion resection in an undefined number of participants. Functional outcome was achieved in 39.8% of the 241 participants assigned to the standard trauma craniectomy group and in 28.6% of the limited craniectomy group. The most important conclusion of this study was that a large craniectomy was associated with a significantly better outcome and reduced ICP than a smaller craniectomy.
Moein 2012	**RCT. Excluded due to ineligible intervention (DC was primary rather than secondary).** Small (n = 20) single-center RCT which included patients with severe TBI (GCS ≤ 8) with midline shift or basal cistern effacement in a brain CT scan. P-DC was performed in these patients before ICP monitoring. The treatment group (n = 10) received DC and medical treatment and the control group (n = 10) medical treatment only. Mortality was 30% in the control group and 10% in the treatment group.
Qiu 2009	**RCT. Excluded due to ineligible intervention and comparator (DC was primary rather than secondary).** The study compared the effectiveness of 2 different types of primary unilateral decompressive procedures in adults (18 to 65 years) with severe TBI (GCS ≤ 8 at admission), and unilateral brain swelling. Brain swelling was defined as a midline shift > 5 mm, cerebral contusions < 25 mL and compressed basal cisterns on the CT scan. This category of patients correspond to the diffuse injury type IV of the Marshall's classification. However, in the summary of results, patients with categories III to VI were included in both groups.
Wang 2014	**Quasi-RCT. Excluded due to ineligible intervention and comparator.** Quasi-randomized trial (allocation was alternate). Comparison of two different surgical techniques to decompress the brain in patients with severe TBI and heterogenous conditions such as diffuse brain swelling, large volume hematoma, uni- or bilateral dilated and unreactive pupils. There was no 'standard care' arm. 128 participants were assigned sequentially to receive either 'controlled decompression' - a form of craniotomy in which ICP is gradually released - or conventional DC. The study reported a statistically non-significant reduction in the incidence of intraoperative acute brain swelling in participants who received the novel treatment compared with those who had conventional DC.
Wen 2007	**RCT. Excluded due to ineligible intervention and comparator (2 types of P-DC).** A single-center RCT in which patients with mild, moderate, or severe TBI and hemorrhagic mass lesions were operated on using conventional P-DC decompressive surgery (40 patients) or P-DC using a modified decompressive technique (48 patients). Inclusion and exclusion criteria were not specified.
Zhao 2016	**Protocol for an RCT. Excluded (rather than placed in 'ongoing studies') due to ineligible intervention and comparator.** Protocol for a RCT (PRECIS trial) to test whether therapeutic DC performed on the basis of emergence of intra-operative brain swelling (P-DC in the terms of this re-

Study	Reason for exclusion
	view), results in a better outcome than CO conducted in patients with severe TBI (GCS score ≤ 8) and postoperative malignant intracranial hypertension.
Zhao 2018	**RCT. Excluded due to ineligible intervention/population (P-DC).** Investigators compared the outcome of participants with severe TBI who underwent early primary bilateral DC (n = 42) compared with those managed by medical treatment and secondary DC if required (n = 50). Authors concluded that early bilateral decompressive craniectomy for TBI reduced ICP, improved outcome and improved the patients' quality of life compared with conventional management.

Abbreviations
CT: computed tomography
CO: craniotomy
DC: decompressive craniectomy
GCS: Glasgow Coma Scale
ICP: intracranial pressure
P-DC: primary decompressive craniectomy
TBI: traumatic brain injury

Characteristics of ongoing studies *[ordered by study ID]*

RANDECPED 2019

Trial name or title	**NCT03766087:** Decompressive craniectomy for severe traumatic brain injury in children with refractory intracranial hypertension (RANDECPED)
Methods	**RCT**
Participants	**Inclusion criteria** • < 18 years of age • Severe traumatic brain injury (initial GCS < 9) • Accidental trauma • Refractory intracranial hypertension: ICP > 20 mmHg over 30 minutes for children > 1 year of age and ICP > 15 mmHg over 30 minutes for children < 1 year of age. • Received optimal medical management • Affiliation with a social security scheme • Signed informed consent provided by the two holders of parental authority **Exclusion criteria** • Inflicted cranial trauma (e.g. shaken baby syndrome) • Patients having an initial surgery for removal of an intracranial hemorrhagic collection of blood (e.g. a subdural hematoma, extradural hematoma, and intraparenchymal hematoma) for which the flap was not replaced. • Pregnancy
Interventions	**Intervention:** DC plus optimal medical management of intracranial pressure **Comparator:** optimal medical management of ICP only
Outcomes	**Primary outcomes** • Functional neurological status 2 years after surgery Functional neurological status (equating with success of the treatment) will be measured by the Glasgow Outcomes Scale-Extended Pediatric version. **Secondary outcomes**

RANDECPED 2019 *(Continued)*

- Progression of ICP at 24 hours, i.e. the difference between the values of ICP at inclusion and 24 h after inclusion
- Functional neurological status of the patients at 1 year: will be measured by the Glasgow Outcomes Scale-Extended Pediatric version.
- Evaluation of overall cognitive functioning at 1 and 2 years: neuropsychological assessment will use the Wechsler intelligence scales (IQ tests) which include five tests:
  - verbal comprehension index;
  - fluid reasoning index;
  - working memory index;
  - processing speed index; and
  - a total IQ.
- Description of surgical parameters of participants with successful craniectomy upon admission to resuscitation to describe the predictive factors of successful craniectomy.
- Description of clinical parameters of participants with successful craniectomy upon admission to resuscitation to describe the predictive factors of successful craniectomy.
- Description of radiological parameters patients with successful craniectomy upon admission to resuscitation to describe the predictive factors of successful craniectomy.
- Number of adverse events linked to surgery
- Overall survival: the survival time will be defined as the time between the date of the cranial trauma and when death occurs from all causes combined.
- Quality of life: measured at 3 months, 1 year and 2 years by Lansky scale.

Starting date	**September 2019**
Contact information	**Principal Investigator:** Michel Lonjon, Pr. Hôpitaux Pédiatriques de Nice CHU-LENVAL. **Email:** lonjon.m@chu-nice.fr **Tel:** 0033492037958
Notes	**Estimated primary completion date:** January 2023 (Final data collection date for primary outcome measure)

Abbreviations
DC: decompressive craniectomy
GCS: Glasgow Coma Scale
ICP: intracranial pressure
IQ: Intelligence Quotient
RCT: randomized controlled trial

DATA AND ANALYSES

Comparison 1. Decompressive craniectomy versus medical treatment only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Mortality at 1 month	1	27	Risk Ratio (M-H, Random, 95% CI)	0.54 [0.17, 1.72]
1.2 Mortality at 6 months	3	571	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.43, 1.01]
1.3 Mortality at 12 months	1	373	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.45, 0.76]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 GOS: Death/vegetative state vs other outcomes	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Death/vegetative state vs other outcomes at 6 months	2	544	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.46, 2.13]
2.2 Death/vegetative state vs other outcomes at 12 months	1	373	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.54, 0.86]
3 GOS: 'Unfavourable outcome' as per RESCUEicp	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 'Unfavorable outcome' as per RESCUEicp at 6 months	2	544	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.69, 1.63]
3.2 'Unfavorable outcome' as per RESCUEicp at 12 months	1	373	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.69, 0.95]
4 GOS: 'Unfavorable outcome' on GOS as per original Cochrane protocol	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 'Unfavorable outcome' as per protocol at 6 months	3	571	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.71, 1.40]
4.2 'Unfavorable outcome' as per protocol at 12 months	1	373	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.83, 1.09]
5 Changes in ICP from randomization to 48 hours	2	182	Mean Difference (IV, Random, 95% CI)	-4.66 [-6.86, -2.45]

Analysis 1.1. Comparison 1 Decompressive craniectomy versus medical treatment only, Outcome 1 Mortality.

Study or subgroup	Decompressive craniectomy n/N	Medical treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 Mortality at 1 month					
Taylor 2001	3/13	6/14		100%	0.54[0.17,1.72]
Subtotal (95% CI)	**13**	**14**		**100%**	**0.54[0.17,1.72]**
Total events: 3 (Decompressive craniectomy), 6 (Medical treatment)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.04(P=0.3)					
1.1.2 Mortality at 6 months					
Taylor 2001	3/13	6/14		11.8%	0.54[0.17,1.72]
DECRA 2011	14/73	15/82		28.01%	1.05[0.54,2.02]
RESCUEicp 2016	54/201	92/188		60.19%	0.55[0.42,0.72]
Subtotal (95% CI)	**287**	**284**		**100%**	**0.66[0.43,1.01]**
Total events: 71 (Decompressive craniectomy), 113 (Medical treatment)					

Favors DC 0.05 0.2 1 5 20 Favors medical treatment

Study or subgroup	Decompressive craniectomy	Medical treatment	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI

Heterogeneity: Tau²=0.06; Chi²=3.24, df=2(P=0.2); I²=38.26%

Test for overall effect: Z=1.9(P=0.06)

1.1.3 Mortality at 12 months

| RESCUEicp 2016 | 59/194 | 93/179 | | 100% | 0.59[0.45,0.76] |
| **Subtotal (95% CI)** | **194** | **179** | | **100%** | **0.59[0.45,0.76]** |

Total events: 59 (Decompressive craniectomy), 93 (Medical treatment)

Heterogeneity: Not applicable

Test for overall effect: Z=4.11(P<0.0001)

Test for subgroup differences: Chi²=0.24, df=1 (P=0.89), I²=0%

Favors DC 0.05 0.2 1 5 20 Favors medical treatment

Analysis 1.2. Comparison 1 Decompressive craniectomy versus medical treatment only, Outcome 2 GOS: Death/vegetative state vs other outcomes.

Study or subgroup	Decompressive craniectomy	Medical treatment	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI

1.2.1 Death/vegetative state vs other outcomes at 6 months

DECRA 2011	23/73	17/82		45.04%	1.52[0.88,2.61]
RESCUEicp 2016	71/201	96/188		54.96%	0.69[0.55,0.87]
Subtotal (95% CI)	**274**	**270**		**100%**	**0.99[0.46,2.13]**

Total events: 94 (Decompressive craniectomy), 113 (Medical treatment)

Heterogeneity: Tau²=0.27; Chi²=6.91, df=1(P=0.01); I²=85.54%

Test for overall effect: Z=0.04(P=0.97)

1.2.2 Death/vegetative state vs other outcomes at 12 months

| RESCUEicp 2016 | 71/194 | 96/179 | | 100% | 0.68[0.54,0.86] |
| **Subtotal (95% CI)** | **194** | **179** | | **100%** | **0.68[0.54,0.86]** |

Total events: 71 (Decompressive craniectomy), 96 (Medical treatment)

Heterogeneity: Not applicable

Test for overall effect: Z=3.26(P=0)

Test for subgroup differences: Chi²=0.8, df=1 (P=0.37), I²=0%

Favors DC 0.01 0.1 1 10 100 Favors medical treatment

Analysis 1.3. Comparison 1 Decompressive craniectomy versus medical treatment only, Outcome 3 GOS: 'Unfavourable outcome' as per RESCUEicp.

Study or subgroup	Decompressive craniectomy	Medical treatment	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI

1.3.1 'Unfavorable outcome' as per RESCUEicp at 6 months

DECRA 2011	41/73	34/82		44.51%	1.35[0.98,1.88]
RESCUEicp 2016	115/201	123/188		55.49%	0.87[0.75,1.02]
Subtotal (95% CI)	**274**	**270**		**100%**	**1.06[0.69,1.63]**

Total events: 156 (Decompressive craniectomy), 157 (Medical treatment)

Favors DC 0.5 0.7 1 1.5 2 Favors medical treatment

Study or subgroup	Decompressive craniectomy	Medical treatment	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI

Heterogeneity: Tau²=0.08; Chi²=5.65, df=1(P=0.02); I²=82.3%

Test for overall effect: Z=0.28(P=0.78)

1.3.2 'Unfavorable outcome' as per RESCUEicp at 12 months

| RESCUEicp 2016 | 106/194 | 121/179 | | 100% | 0.81[0.69,0.95] |
| **Subtotal (95% CI)** | **194** | **179** | | **100%** | **0.81[0.69,0.95]** |

Total events: 106 (Decompressive craniectomy), 121 (Medical treatment)

Heterogeneity: Not applicable

Test for overall effect: Z=2.55(P=0.01)

Test for subgroup differences: Chi²=1.36, df=1 (P=0.24), I²=26.44%

Favors DC 0.5 0.7 1 1.5 2 Favors medical treatment

Analysis 1.4. Comparison 1 Decompressive craniectomy versus medical treatment only, Outcome 4 GOS: 'Unfavorable outcome' on GOS as per original Cochrane protocol.

Study or subgroup	Decompressive craniectomy	Medical treatment	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI

1.4.1 'Unfavorable outcome' as per protocol at 6 months

Taylor 2001	6/13	12/14		18.32%	0.54[0.29,1.01]
DECRA 2011	51/73	42/82		37.11%	1.36[1.05,1.77]
RESCUEicp 2016	146/201	138/188		44.56%	0.99[0.88,1.12]
Subtotal (95% CI)	**287**	**284**		**100%**	**1[0.71,1.4]**

Total events: 203 (Decompressive craniectomy), 192 (Medical treatment)

Heterogeneity: Tau²=0.06; Chi²=9.1, df=2(P=0.01); I²=78.03%

Test for overall effect: Z=0.02(P=0.99)

1.4.2 'Unfavorable outcome' as per protocol at 12 months

| RESCUEicp 2016 | 132/194 | 128/179 | | 100% | 0.95[0.83,1.09] |
| **Subtotal (95% CI)** | **194** | **179** | | **100%** | **0.95[0.83,1.09]** |

Total events: 132 (Decompressive craniectomy), 128 (Medical treatment)

Heterogeneity: Not applicable

Test for overall effect: Z=0.73(P=0.47)

Test for subgroup differences: Chi²=0.06, df=1 (P=0.8), I²=0%

Favors DC 0.5 0.7 1 1.5 2 Favors medical treatment

Analysis 1.5. Comparison 1 Decompressive craniectomy versus medical treatment only, Outcome 5 Changes in ICP from randomization to 48 hours.

Study or subgroup	Decompressive craniectomy		Medical treatment		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI		Random, 95% CI
Taylor 2001	13	17.4 (3.4)	14	21.9 (8.5)		20.91%	-4.5[-9.32,0.32]
DECRA 2011	73	14.4 (6.8)	82	19.1 (8.9)		79.09%	-4.7[-7.18,-2.22]
Total ***	**86**		**96**			**100%**	**-4.66[-6.86,-2.45]**

Favors DC -20 -10 0 10 20 Favors medical treatment

Study or subgroup	Decompressive craniectomy		Medical treatment		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI		Random, 95% CI
Heterogeneity: Tau²=0; Chi²=0.01, df=1(P=0.94); I²=0%							
Test for overall effect: Z=4.14(P<0.0001)							

Favors DC   -20 -10 0 10 20   Favors medical treatment

ADDITIONAL TABLES

Table 1. Annotated bibliography

Reference ID	Narrative summary
Aarabi 2006	This single-center retrospective study evaluated the effects of DC on the outcome of 50 patients with severe TBI and brain swelling operated on over a period of 5 years (2000-2004). Seventeen patients were operated on within 48 h of injury (34%). In all but 1 patient, a fronto-parieto-temporal unilateral decompression and an expansive duraplasty were performed. The cumulative probability of survival in the first 30 days after DC was 77.6%. Of the 39 patients who survived, 20 (51.3%) had a good outcome according to the dichotomized GOS.
Abdullah 2005	A prospective non-controlled study of 17 severe TBI patients who underwent DC and in whom intracranial compliance was evaluated before and after DC. Intracranial compliance improved dramatically in all patients who received DC and survived.
Albanese 2003	Retrospective cohort study of the DCs performed in a university hospital during a 5-year period. Both P-DC (27 patients) and DC (13 patients) were included. Secondary craniectomy was performed in patients with intractable intracranial hypertension and ICP above 35 mmHg. Outcome was determined by the GOS score obtained at 12 months. The surgical procedure was chosen according to the site of the cerebral lesion. Bilateral DC was performed when the CT scan showed diffuse edema without a mass lesion. When a patient showed hemispheric edema, unilateral DC was performed. Duraplasty was carried out with autologous fascia. All participants included in the study had unilateral or bilateral unreactive pupils.
Alexander 1987	Retrospective study of 15 patients with severe TBI who underwent DC. In all patients a bilateral subtemporal craniectomy was performed. ICP was immediately reduced in 13 of the 15 patients. Of the 13 surviving patients, 7 were independent.
Al-Jishi 2011	Single-center restrospective study conducted in a first level trauma center (Montreal General Hospital-McGill University Health Centre, Canada) in a 4-year period (2004-2008). The study evaluated the differences between patients in whom P-DC was conducted from those in whom S-DC was used to manage high 'refractory' ICP. Seventy patients were operated, 44 with P-DC and 26 with S-DC. There was a significant difference in the mechanism of injury, neurological severity at baseline and in the Marshall grade between patients in both groups. Outcome was also different. Primary DC showed 45.5% good outcome and 40.9% mortality and secondary DC 73.1% good outcome and 15.4% mortality.
Alvis-Miranda 2013	Narrative review in which the history, indications, technical aspects, complications and cost-effectiveness of DC are updated.
Ammar 1993	Case series of 5 pediatric patients with severe brainstem dysfunction in whom decompressive surgery was performed. All were suffering from compression of the brain stem and experienced return of brain stem function following decompressive surgery.
Barthelemy 2016	Systematic review including RCTs, nonrandomized studies, and case series. Studies written in languages other than English, French, Spanish, Italian, and German were excluded. Authors concluded that DC does not result in better outcomes than maximal medical trreatment in patients with

Table 1.   Annotated bibliography *(Continued)*

	severe TBI. However, data from nonrandomized studies suggested that younger age, higher GCS score, and very short interval between TBI and surgery may have a positive impact on outcome.
Beez 2019	Retrospective study covering the years 2010–2018 in a single center in Germany including patients < 18 years. Fifteen children (mean age 12 years, range 1 to 17 years) underwent DC for TBI (n = 12), intracerebral hemorrhage (n = 2), or ischemic stroke (n = 1).
Berger 2002	Two case reports of pediatric patients managed with hypertonic saline and decompressive surgery.
Bohman 2013	Narrative review of the topic of DC in the management of TBI. The paper comments on two studies included in this review.
Bonaventure 2018	Abstract presented in 2018. No subsequent publication identified thereafter. Results published in the paper. Aim was to assess efficacy and safety of DC in adult patients with severe traumatic brain injury. Authors included 3 trials for a total of 573 patients. They observed no effects of DC on outcome measured by the GOS with the use of DC (RR 1.03, 95% CI 0.74 to 1.44), mortality (RR 0.66, 95% CI 0.40 to 1.10) or ICU length of stay. DC decreased mean ICP (-3.73, 95% CI -5.78 to -1.68). Authors also found an increased incidence of patients with complications (RR 1.95, 95% CI 1.32 to 2.89). Authors concluded that evidence did not support the use of DC as a standard care intervention in adult patients with severe TBI.
Bor-Seng-Shu 2012	Systematic review and meta-analysis including retrospective and non-randomized prospective studies without a control group. A total of 479 patients with ICP. Neither neurological outcome nor mortality was included in the studied variables and a risk of bias analysis was not conducted. No control group was established and patients were used as their own controls (ICP analyzed before and after DC). Despite these limitations, the review showed that DC is effective in reducing ICP and increasing CPP. Weighted mean difference in ICP before and after surgery was 17.59 mmHg (95% CI −11.23 to 23.435).
Bose 2002	Description and discussion of a short series of 3 adult patients with TBI who underwent DC after medical treatment failed to control ICP. The authors used this series to discuss how the outcome of DC is related to factors such as the timing of surgery, patient age, GCS score, level of ICP, and some neuroradiological findings. They recommended decompressive surgery when ICP exceeds 50 mmHg despite maximal medical treatment.
Britt 1978	Retrospective study of 42 patients, with severe, moderate, or mild head injury and acute subdural hematoma who underwent surgery within 24 hours of arrival at the emergency room. The majority (36) had severe injuries. P-DC was performed in 32 patients because the brain was "swollen and edematous at the completion of clot removal".
Burkert 1988	Narrative review published in German. This review emphasized the need for early surgery and large bone decompression to obtain good results.
Chen 2011	Retrospective study conducted in a single institution including 102 patients with severe TBI (GCS 4 to 8) and an acute subdural hematoma. Forty-two patients (41%) were treated with standard craniotomy and 60 (58.8%) with P-DC. Both surgical strategies achieved the same neurological outcome.
Chibbaro 2007	Single-center retrospective study of 48 patients (30 men and 18 women) with a mean age of 47 years who underwent DC with an augmentative duraplasty. These patients underwent DC when ICP was > 25 mmHg for > 30 minutes, despite first-tier therapeutic measures. Twenty-five patients (55%) achieved a favorable outcome in the dichotomized GOS scale. Outcome was evaluated at a mean follow-up of 14 months after TBI.
Cho 1995	Retrospective study of 10 children under 2 years of age with acute shaken or impact baby syndrome treated by uni- or bilateral secondary decompressive surgery.

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Table 1. Annotated bibliography *(Continued)*

Citerio 2007	Narrative review of the role of DC in the management of refractory high ICP in patients with severe TBI and other neurocritical patients.
Clark 1968	This study is probably one of the most influential in the neurosurgical literature despite the fact that the authors reported on only 2 patients operated on in the pre-CT scan era. This is a pessimistic report based on the authors' experience with 2 patients who underwent circumferential craniectomy and opening of the dura mater with the idea of expanding the whole cranial vault.
Cooper 1976	A classical and much cited paper reporting hemicraniectomy in acute subdural hematomas. This was a retrospective analysis over a 3-year period of 50 patients with a large subdural hematoma with or without associated brain swelling who underwent P-DC. Angiography or neurological examination alone were used for the diagnosis.
Coplin 2001	Non-randomized pilot clinical trial performed at a single institution. Primary decompressive hemicraniectomy and augmentative duraplasty, with bovine pericardium, was used to treat patients whose CT scan showed a degree of midline shift that was disproportional to the volume of a surgically evacuable mass lesion. The main goal of this study was to compare the outcomes of traditional craniectomy versus craniectomy with duraplasty as the initial intervention to control the effects of early brain swelling after severe TBI. The study population was highly selected and patients aged > 40 years with abnormal motor response were excluded. The type of decompressive flap was determined by the participating surgeons before surgery. In this study DC reduced mortality while yielding similar neurological outcomes for survivors.
Csokay 2002	Retrospective study of patients with severe TBI treated with DC and a new surgical technique to protect the venous system, called vascular tunnel. Patients were treated when ICP was above the 30 mmHg threshold and their outcomes were compared with a historical control group of medically treated patients.
Dam-Hieu 1996	Two case reports of children with refractory high ICP successfully treated by DC with a favorable outcome.
De Luca 2000	A single-center retrospective study of 22 patients who underwent DC with dural graft augmentation. Decompressive surgery was indicated when ICP was above a threshold of 30 mmHg and was not controllable with medical treatment, including mild hypothermia and/or barbiturates in some patients.
Diemath 1966	Retrospective study, published in German, analyzing results from a group of patients in whom bitemporal decompressive surgery was performed for severe brain trauma.
Eghwrudjakpor 2010	Narrative review of the history and indications of DC in traumatic brain injury.
El-Watidy 2005	A case report of a 6-month old infant with a moderate TBI who presented with neurological worsening because of secondary bilateral ischemic brain damage and high ICP that was refractory to medical treatment. A bifrontal DC was performed.
Faleiro 2005	Brazilian single-center retrospective study (published in Portuguese) of 21 patients with severe or moderate TBI who underwent DC very early after injury (within 6 hours). Due to the limited availability of ICP monitoring in the institution where the trial was conducted, the criteria to perform DC for most patients were based on CT scan findings (midline shift, basal cisterns effacement, etc.). Hydrocephalus within the first month after DC was the most frequent complication found (28.5% of the patients). Eleven patients (52.5%) achieved a good outcome on the GOS.
Faleiro 2006	Retrospective study of 7 pediatric patients (2 to 17 years old) with severe TBI, treated with unilateral DC due to increased ICP. 6 months after injury 3 patients had died, 1 was in a vegetative state, and 3 achieved good recovery.
Faleiro 2008	Single-center retrospective study of a cohort of 89 patients in a Brazilian institution. 2 different cohorts were differentiated in this study:

Table 1. Annotated bibliography *(Continued)*

- 68 patients who underwent early surgery based on the CT scan findings (effacement of basal cisterns, midline shift, etc.); and
- 21 patients who underwent ICP monitoring in whom maximal medical treatment, including barbiturates, failed to control ICP.

Fatima 2019	A `meta-analysis` to determine the efficacy of P-DC performed at the time of mass lesion evacuation and standard medical care with (secondary) DC when medical management of raised ICP failed to improve the clinical outcome in TBI. This meta-analysis included 7 RCTs, case–control studies (CCSs) and cohort studies (CS) and participants with both moderate and severe TBI. The 3 studies included in the present Cochrane Review were also included; however, the purpose of the study, the type of included studies and the way the results were pooled do not allow a reasonable comparison of the two analyses.
Figaji 2003	Retrospective study of a group of 5 pediatric patients (< 15 years) with severe TBI and diffuse brain injury who underwent decompressive surgery based on clinical criteria and CT scan findings suggestive of increased ICP (midline shift, effacement of basal cisterns, etc.). No preoperative ICP monitoring was conducted in this study. Surgical technique was very heterogeneous. While in some patients the bone flap was removed, in others it was replaced.
Figaji 2007	Case report of a 5-year-old boy who sustained an isolated severe head injury. This patient had a diffuse bilateral brain swelling and high ICP that could not be controlled with first-tier therapeutic measures. The decision to conduct decompressive surgery was taken because the brain tissue oxygen pressure (PtiO$_2$) decreased while ICP increased. Immediately after DC, PtiO$_2$ increased significantly, particularly when the dura mater was opened. These changes were sustained throughout the monitoring period and the patient achieved a good functional outcome.
Fourcade 2006	Narrative review (published in French) on the background, rationale, surgical technique, indications, and complications of DC in TBI.
Gaab 1990	Prospective single-center, non-randomized study reporting the results of uni- or bilateral secondary decompression in a cohort of 37 adult and pediatric patients with severe TBI that was unresponsive to medical treatment to control ICP. Clinical criteria were very strict, including only patients < 40 years and with motor response. Patients with bilateral non-reactive pupils, space-occupying lesions, or large infarctions in the CT scan were excluded. Large bilateral fronto-parieto-temporal bone flaps were performed in 19 cases and unilateral craniectomy was performed in 18. The dura mater was opened and duraplasty was performed using temporal muscle and fascia. The mean age of this cohort was 18 ± 7 years (4 to 34 years). 8 patients were included in the bad outcome category (21%) and 29 in the good outcome category.
Garg 2019	This meta-ananalysis included 4 studies, including the 3 within the present review, in addition to Moein 2012, which we excluded (see 'Characteristics of excluded studies' section). Despite these differences, the results were similar to ours; viz; that DC decreases mortality compared with best medical management but survivors have a higher incidence of poor neurological outcome.
Gerl 1980	Retrospective study of 30 patients who underwent a secondary bilateral fronto-temporo-parietal craniectomy with opening of the dura mater. Patients with TBI and other pathologies (venous sinus thrombosis) were included. Of the 30 patients: 21 died, 4 remained in a vegetative state, and only 5 presented with functional survival.
Goettler 2008	Letter to the Editor regarding the so-called 'Tucci flap' or 'hinge craniectomy' employed by different surgeons (Schmidt 2007). This surgical procedure was based on replacing the bone flap in DC using a technique that allows some expansion of the swollen brain without the need for cranioplasty.
Göksu 2012	A retrospective analysis of a subgroup of 28 patients operated with bilateral dilated and unreactive pupils. This group represented 19% of 147 patients who underwent DC in a single institution during a 5-year period. The overall mortality of this operated group was 62% but 4 of the surviving patients were independent 1 year after injury.

Table 1. Annotated bibliography *(Continued)*

Gouello 2014	Single-centre, retrospective study of 60 patients with a severe TBI who underwent P-DC or DC (unilateral or bilateral) between January 2005 and May 2011. 40 patients were operated to manage refractory high ICP and 20 received P-DC. Patients were selected for DC when ICP > 20 mmHg and CPP was < 65 mmHg and before the administration of barbiturates as a second-tier therapy. 60% of patients in whom DC was conducted achieved a favorable functional outcome (good recovery or moderate disability in the GOS) 24 months after injury.
Gower 1988	Retrospective study of a cohort of 115 selected severe TBI patients with no evidence of mass lesion on admission and who underwent ICP monitoring. 10 of these had high ICP refractory to medical treatment. Barbiturates were used In 7 of these 10 patients. Bilateral subtemporal craniectomy was performed in all cases and the dura was opened in a stellate fashion. In 4 patients temporal tip lobectomy was performed. Mortality was higher in patients with high ICP refractory to barbiturates than in those who underwent bilateral decompression (82.4% versus 40%, respectively).
Grindlinger 2016	Single center, retrospective, observational study; 31 patients aged 16 to 72 years of either sex who sustained a severe, non-penetrating TBI underwent a unilateral DC for evacuation of parenchymal or extra-axial hematoma or for failure of medical therapy to control ICP. Authors concluded that unilateral DC is an option in patients with high ICP and that this procedure is associated with acceptable-mortality good functional outcome.
Guerra 1999a	Prospective, single-center, non-randomized study in a highly selected cohort of 57 patients with severe TBI, aged < 30 years and without clinical signs of devastating primary brain damage. All patients presented signs of diffuse uni- or bilateral brain swelling on the first CT scan or developed massive brain swelling after surgical evacuation of a mass lesion. 17 patients did not undergo placement of an ICP monitor and underwent surgery on the basis of signs of either clinical deterioration or CT scan findings after admission (P-DC). Uni- or bilateral decompression with duraplasty was performed depending on the CT scan findings.
Guerra 1999b	Narrative review with annotated bibliography on the topic.
Hejazi 2002	Prospective study of 7 pediatric patients (5 to 14 years) with severe TBI, abnormal extensor motor response, diffuse bilateral brain swelling, and high ICP (range 46 mmHg to 55 mmHg) who underwent unilateral DC.
Ho 2008	Prospective observational study with the aim of investigating the effect of DC on cerebral oxygenation, cerebrovascular reactivity, and brain neurochemistry in patients with severe TBI. 16 patients underwent bifrontal or unilateral DC and expansive duraplasty when maximal medical treatment, including the administration of barbiturates, failed to maintain ICP below 20 mmHg. DC significantly reduced ICP in all patients regardless of outcome. Mortality at 6 months was 37.5% and 5 patients (31%) achieved a favorable outcome in the dichotomized GOS. An interesting finding in this study was that patients with a favorable outcome presented a significant improvement both in tissue oxygenation and brain energetic metabolism evaluated by microdialysis in the most affected hemisphere after DC. In contrast, patients with an unfavorable outcome demonstrated no significant, or only marginal, improvements in both oxygenation and brain metabolism.
Holland 2004	Narrative review of indications and surgical techniques of DC to treat refractory high ICP after TBI.
Honeybul 2010	Retrospective study comparing the observed and predicted outcome based on the CRASH model outcome (MRC 2008) of 147 patients with severe TBI who underwent DC in Western Australia between 2004 and 2008. The study showed that a significant proportion of patients had a better than predicted neurological outcome.
Hutchinson 2004	A comprehensive narrative review of the indications of DC in the management of severe TBI.
Hutchinson 2005	An editorial that reviewed the recent advances in decompressive surgery and called for a multicenter randomized controlled trial to evaluate this therapeutic option.
Hutchinson 2011b	Editorial comment on a non-randomised clinical trial (Al-Jishi 2011)

Table 1. Annotated bibliography *(Continued)*

Jagannathan 2007	A retrospective study of 23 pediatric patients (mean age 11.9 years, range 2 to 19 years) with severe TBI who underwent DC at a single institution over a 10 year period (January 1995 to April 2006). Decompressive surgery was used for patients where high ICP remained refractory (> 20 mmHg) despite aggressive medical treatment. Unilateral hemicraniectomy or bifrontal decompressive surgery with opening of the dura mater and augmentative duraplasty was conducted depending on CT scan findings. Authors reported a 31% rate of mortality and an 82% rate of favorable outcome 2 years after injury.
Josan 2006	A retrospective review of all pediatric patients treated in a single center in a 3-year period. All patients had refractory high ICP after an isolated head injury. In patients with refractory ICP further management varied according to the attending neurosurgeon in charge of the case. Some of the patients underwent an early DC whereas others were treated with a variable combination of hypothermia and barbiturate coma; 12 patients were included. DC was carried out by raising a large unilateral or bilateral bone flap but without opening the dura mater. 6 patients underwent DC and 6 received maximal medical therapy. All patients who underwent DC and 4 in the non-operative group were alive 1 year after injury.
Jourdan 1993	Case series of 9 comatose patients with hemispheric unilateral edema secondary to ischemic stroke (8 patients) and associated with traumatic acute subdural hematoma (1 patient) who underwent DC.
Kan 2006	Retrospective review of the trauma registry at a single center to identify children with severe TBI who underwent P-DC or (secondary) DC between 1996 and 2005; 51 children were identified, of whom 45 underwent a P-DC in conjunction with removal of a mass lesion. 6 patients underwent DC for refractory high ICP, and 5 of them died. Authors did not recommend DC for refractory ICP in patients with no mass lesion. An important bias of this study was that all patients who underwent DC had an ICP > 40 mmHg and most had uni- or bilateral fixed pupils before surgery.
Karlen 1987	Authors reported on 7 patients with severe TBI and high ICP refractory to barbiturates who were treated with DC to control ICP. Study published in German.
Kawamata 2007	Narrative review (published in Japanese) discussing the role of DC in patients with diffuse brain injuries and refractory high ICP.
Kerr 1968	Report of 2 patients with the angiographic diagnosis of diffuse brain edema who underwent bone decompression. Both patients died despite temporary improvement after surgery. The authors emphasized the need to perform huge bilateral decompression with dural graft and temporal decompression down to the base of the temporal bone in order to achieve a maximum increase in volume.
Kjellberg 1971	Retrospective study of 73 adult and pediatric patients (age 3 to 84 years); 50 of the 73 patients had severe TBI, while the remainder had spontaneous subarachnoid hemorrhage, massive infarction, or gunshot wounds.
Kolias 2012	Report of the results of a survey of neurosurgeons across Europe on the frequency of their use of P-DC in the management of acute subdural hematomas that underwent surgical evacuation. In this survey it was found that one-third of the neurosurgeons used P-DCs in > 50% of these patients.
Kolias 2018	Narrative review, reviewing the use of DC in TBI. Both DECRA 2011 and RESCUEicp 2016 were included. Authors concluded that the former showed that neuroprotective bifrontal DC for moderate intracranial hypertension is not helpful; however, they concluded that last-tier DC for severe and refractory intracranial hypertension can significantly reduce the mortality rate but is associated with a higher rate of disability. Additionally, the role of P-DC when evacuating an acute subdural hematoma and the ISRCTN87370545 randomized trial is discussed.
Kontopoulos 2002	Retrospective study of 9 patients from a total of 100 admissions for severe head injury who underwent uni- or bilateral DC when ICP was refractory to maximum medical therapy.

Table 1. Annotated bibliography *(Continued)*

Kramer 2016	A cohort study assessing 644 consecutive patients with moderate to severe TBI. Indications for DC were compared with enrolment criteria for the DECRA 2011 and RESCUEicp 2016 trials. Most DC procedures, (67%) were P-DC performed concomitantly with evacuation of a space-occupying lesion. ICP measurements influenced the decision to perform DC in 18% of patients. Authors concluded that the results of DECRA and REscueICP do not directly apply to a large proportion of patients undergoing DC in practice.
Kunze 1998	Retrospective study of 28 patients with a moderate or severe TBI (GCS score ≤ 12) and ICP unresponsive to maximum conservative treatment (including barbiturates) who underwent uni- or bilateral DC.
Lacerda 2004	Single-center retrospective review of a cohort of 21 patients with severe TBI who underwent uni-or bilateral DC when ICP was refractory to maximal medical treatment.
Lee 2003	A single-center retrospective study of 38 patients who underwent DC to treat increased refractory ICP. All 38 had high ICP, 28 had TBI, 4 had spontaneous intracerebral hematoma, 4 had brain infarction, and 2 had brain tumors.
Makino 1979	A series of 207 patients who underwent large uni- or bilateral DC. These patients were also included in the series published in Yamaura 1979.
Meier 2000	A single-center retrospective study of a cohort of 19 patients who underwent P-DC (11 patients) or (secondary) DC (8 patients).
Meier 2003a	Retrospective study of a series of 50 patients who underwent DC at a single institution. In this series, patients were operated on after failure of conservative treatment and by following very strict selection criteria.
Meier 2003b	Retrospective analysis of a cohort of 80 adult patients with TBI who underwent DC. In a first group of 53 patients, a P-DC was performed when generalized brain edema was evident during surgery indicated for removal of space-occupying lesions (subdural, epidural hematoma, brain contusion, etc.). In a second group of 27 patients with TBI, DC was indicated when conservative treatment failed to control ICP. Outcome of both groups in this study were analyzed together, therefore analysis of the outcome for DC could not be conducted.
Mhanna 2015	Retrospective pediatric case-control study conducted in a single-center pediatric ICU between May 1998 and May 2008 in children with severe TBI and treated with DC. Patients were matched to patients who were treated medically without DC. There were no differences between DC and control patients regarding age (10.2 ± 5.9 years vs 12.4 ± 5.4 years, respectively). There were no significant differences in survival between patients with DC and controls (71% 12/17 vs 82% 14/17, respectively; P = 0.34).
Miyazaki 1966	A narrative review published in Japanese regarding the role of bifrontal decompression in the management of traumatic brain edema. The same author published a very similar review in English in 1971 (Miyazaki 1971).
Miyazaki 1971	Narrative review of the problem of traumatic brain edema and its treatment in the 1960s. The author presented the use of a bifrontal DC with opening of the dura mater and sectioning of the superior sagital sinus. The author suggested that this alternative was much better than subtemporal craniectomy (proposed originally by Cushing 1905) in patients with brain edema without evacuable mass lesions. The advantage of decompressing the brain in the direction of the fronto-occipital axis was discussed. In this paper, emphasis was placed on the surgical technique used to conduct bifrontal DC. Miyazaki presented 11 patients treated with this procedure and the dramatic effects of this procedure on ICP measured by lumbar puncture; 8 of the 11 patients survived.
Morgalla 1995	Pediatric case report series of 2 patients with a severe head injury and ICP refractory to medical therapy who underwent bifrontal DC.

Table 1. Annotated bibliography *(Continued)*

Münch 2000	A single-center retrospective study of 49 severely head injured patients (age range 14 to 83 years) who underwent unilateral DC between January 1995 and March 1998. All patients were treated according to a homogeneous and strict protocol based on the Brain Trauma Foundation Guidelines. This study included both primary (31 patients) and secondary (18 patients) decompressive unilateral craniotomies. Mean ICP was significantly reduced from 22.1 ± 11.1 mmHg before craniectomy to 9.7 ± 10.8 mmHg after surgery. For 5 patients, the 6-month outcome was not available. Good outcome at 6 months in 41%.
Nirula 2014	Retrospective study conducted in 11 Level I USA trauma centers between 2008 and 2009. Patients had to be ≥16 years with evidence of closed TBI and an admission GCS score of ≤ 13. In-hospital mortality in patients with high ICP who underwent medical management was compared with mortality of those who had DC performed within 48 h of injury. In this study, P-DC and (secondary) DC were defined differently to the definitions used by us or in previews reviews. There were 2602 patients who met the inclusion criteria, of whom 109 (5%) had a DC that was conducted to control ICP; although authors did not present data for the number of patients who received ICP monitoring or the threshold used to indicate decompressive surgery. Results did not show any clinical benefit with early P-DC compared with the controls (RR, 1.07; 95% CI 0.67 to 1.73; P = 0.77).
Ogawa 1974	Retrospective single-center study of 29 patients with severe TBI and in whom massive acute brain swelling occurred during craniectomy for evacuation of acute subdural hematoma. This paper focused on P-DC and therefore studied a completely different cohort of patients to us (see 'Types of surgical decompression' section). 26 of the 29 patients died and the remaining 3 who survived did so in a vegetative state (described as apallic syndrome in the study).
Ojemann 1966	P-DC in a 12-year old child with a frontal laceration.
Olivecrona 2007	Retrospective single-center study conducted over a 3-year period (1998-2001). The authors attempted to show the benefits of DC in patients with severe TBI treated with what is known as the 'Lund protocol'. These patients had refractory intracranial hypertension (> 25 mmHg) despite Lund therapy that included sodium pentothal aimed at achieving a 'delta' EEG pattern. 21 patients were included in the study out of a total of 93 patients with a severe TBI. Unilateral or bilateral DC was performed based on the CT scan results. Augmentative duraplasty was also performed. The mean age for patients who underwent DC was 39.4 ± 3.4 years. Mean ICP immediately before the craniectomy was 36.4 ± 3.4 mmHg, and was reduced to 13.1 ± 2.1 mmHg after DC. The outcome was favorable (good recovery or moderate disability) in 71% of the patients treated with DC.
Paci 2009	A retrospective single-center study to evaluate the role of P-DC to improve outcome in moderate or severe TBI. 62 of the 197 patients included (31.5%) underwent P-DC and 135 (68.5%) conventional craniotomy. The decision about which technique to perform was made by the neurosurgeon in charge of the patient. After adjusting for the severity of the injury authors did not find any difference in mortality between the 2 groups.
Pereira 1977	Bifrontal DC performed on 12 patients with severe cerebral edema (10 related to cerebral contusion) who did not respond to conventional methods of therapy. Bilateral carotid angiography was the method used for diagnosis.
Piek 2002	Narrative review of DC in TBI.
Polin 1997	A single-institution retrospective case-control study; 35 patients with TBI and diffuse brain injuries, no evacuable mass lesions, and refractory ICP underwent bifrontal DC. The control group consisted of 92 patients enrolled in the American Traumatic Coma Data Bank multicenter study (Marmarou 1991). Patients who had undergone surgery were matched with 1 to 4 control patients based on sex, age, preoperative GCS scores, and maximum preoperative ICP.
Pompucci 2007	A single-center retrospective study that investigated the outcome of 55 patients treated with DC. Age was not an exclusion criterion for DC, so it was possible to analyze the relationship between age and outcome, despite the shortcomings intrinsic to the retrospective nature of the study. The cohort included 2 groups:

Table 1. Annotated bibliography *(Continued)*

- 21 patients who underwent DC because of unilateral or bilateral brain swelling and therapy-resistant intracranial hypertension and/or clinical deterioration; and
- 34 patients with a subdural hematoma together with massive brain edema who underwent P-DC.

Authors pooled cases to analyze 4 established potential predictors of outcome after DC: i.e. sex, age, GCS, and presence of mass lesion. Logistic regression analysis showed age was an independent predictor of outcome. Authors observed that a difference in the outcome existed between patients over 65 and those below 65. However, in the whole population, age was not a discriminating factor for outcome.

Prasad 2015	Retrospective single-center study including 71 pediatric patients with a mean age of 1.6 years. ICP monitoring was only conducted in 33 patients. The threshold ICP for indicating DC was 15 mmHg.
Ransohoff 1971a; Ransohoff 1971b	Prospective study of primary surgical decompression in 35 patients with a severe head injury and acute subdural hematomas. All patients were studied by angiography. Hemicraniectomy and evacuation of the subdural clot were performed. The dura mater was left open and the bone was not replaced after clot removal.
Razack 1997	Retrospective study of 20 adult moderate and severe head-injured patients who underwent bilateral P-DC because of bilateral mass lesions.
Reithmeier 2005	Reported the case of a 10-year old girl in the second week after injury, with multiple post-traumatic intracranial lesions and massive diffuse bilateral brain swelling with high ICP refractory to medical treatment. A bilateral DC was performed and the author reported good recovery 2 years after injury.
Rosenfeld 2007	Letter regarding Aarabi 2006 paper, which emphasizes that there are 2 ongoing multicenter RCTs to test the efficacy of DC in TBI (the DECRA 2011 and RESCUEicp 2016 studies).
Rubiano 2019	A review of the reviews of effectiveness of DC to improve outcomes. Authors used AMSTAR-2 (A MeaSurement Tool to Assess systematic Reviews) (Shea 2017). They found 5 publications, 4 of which included meta-analyses. For mortality, 3 reviews found a positive effect of DC compared to medical management and 2 found no significant difference between groups. The 4 reviews that measured neurological outcome found no benefit of DC. The 2 reviews that assessed ICP both found DC to be beneficial in reducing ICP. DC demonstrated a significant reduction in ICU length of stay in the 1 study that measured it, and a significant reduction in hospital length of stay in the 2 studies that measured that. According to the AMSTAR 2 criteria, the 5 reviews ranged in levels of confidence from low to critically low.
Ruf 2003	Observational pilot study of 6 pediatric patients (age: 5 to 11 years) with severe TBI and high ICP (> 20 mmHg) refractory to medical treatment. In 5 of the 6 patients, the ICP normalized immediately after craniectomy and no secondary elevation was noted. No mortality occurred in this small series.
Rutigliano 2006	Prospective non-controlled study in which 6 pediatric patients (age 13 to 19 years) with moderate or severe TBI and high ICP (> 20 mmHg) unresponsive to maximal medical therapy, including barbiturates, underwent bifrontal or biparietal craniectomies with duraplasty. Upon discharge from hospital, 5 patients were independent or needed minimal assistance.
Schirmer 2008	A comprehensive narrative review of the historic background and the rationale for DC in neurocritical patients, including those with TBI and high ICP refractory to medical treatment.
Schmidt 2007	Report describing a surgical technique for DC in which the bone flap is replaced using titanium miniplates not fixed to the skull, so that the bone flap is mobile. Because the dura mater is left open, a certain degree of brain decompression is allowed. The authors present a retrospective study of 25 patients with TBI and high ICP refractory to medical treatment. Mortality was 48% in this series. No information was given regarding the degree of ICP reduction after this procedure and, according to the terms of this review, a hinge craniotomy should be considered a suboptimal procedure.

Table 1. Annotated bibliography *(Continued)*

Schneider 2002	Retrospective analysis of 62 severely head-injured patients who underwent secondary uni- or bilateral decompressive surgery with dura mater augmentation in a single institution. Selected patients had refractory high ICP (> 40 mmHg in adults and > 25 mmHg in children) and no surgically evacuable mass lesions on the CT scan.
Shigemori 1979	Retrospective study of 15 patients with acute subdural hematoma who underwent P-DC in addition to clot removal. Both pediatric and adult patients were included (age range 5 to 82 years) and 10 of the 15 patients were comatose (GCS was not used in this study).
Shigemori 1980	Retrospective analysis of 15 patients with acute subdural hematoma in whom primary decompressive hemicraniectomy was performed to clarify the beneficial effect and limitation of this operative procedure. Decompressive hemicraniectomy was effective in lowering ICP in all patients, except for the cases that developed acute brain swelling.
Simma 2002	Retrospective single-center study of 8 children (mean age 10 ± 3.5 years), 6 with traumatic head injury and 2 with stroke. 7 underwent bilateral secondary decompression and 1 underwent unilateral secondary hemicraniectomy.
Skoglund 2006	Retrospective study conducted in a referral center with special dedication to the management of severe TBI patients through Lund therapy. 19 patients were included over a 5-year period. 12 of them had received high doses of barbiturates before the decision to perform surgical decompression was taken. Mean ICP was reduced from 29.2 mmHg ± 3.5 mmHg to 11.1 mmHg ± 6.0 mmHg at 1 h after DC and remained significantly lower than baseline at 24 h post-surgery. The relationship between the size of the craniectomy and the decrease in ICP was studied using the Pearson correlation coefficient; a larger craniectomy produced a greater decrease in ICP. The survival rate was 17/19 (89%) and of the surviving patients, 13/19 (68%) had a favorable outcome (GOS 4 or 5), 3/19 (16%) were severely disabled (GOS 3), and 1 patient (5%) was left in a vegetative state.
Spagnuolo 2004	Retrospective study, published in Spanish, of 4 young patients (4 to 46 years) who underwent DC for traumatic diffuse brain injuries with refractory high ICP.
Stefini 2007	Case report of a 32-year-old man with an admission GCS score of 7, a hematoma in the splenium of the corpus callosum, and refractory high ICP. The patient was operated on the 5th day after injury and a bi-occipital DC and a duraplasty were performed. 1 year post-injury, the man was independent in activities of daily living.
Stiefel 2004	Prospective observational study of 5 patients with severe TBI and 2 with spontaneous subarachnoid hemorrhage in a very bad clinical situation who underwent secondary decompressive hemicraniectomy when ICP was refractory (> 20 mmHg) to maximum medical treatment, including barbiturates. In this series, the dura mater was left open. In all but 1 patient, ICP immediately decreased after surgery and in all patients a significant increase in brain tissue oxygen was observed.
Tapper 2017	`Single-center` retrospective study on adult closed TBI patients admitted to a neurosurgical ICU from 2009 to 2012. Patients were divided into 3 groups based on their initial treatment – DC, craniotomy, or conservative treatment. Primary outcome was `6-month` GOS dichotomized to favorable outcome and unfavorable outcome. The association between initial treatment and outcome was assessed using a logistic regression model adjusting for `case-mix` using known predictors of outcome. Patients requiring P-DC had a higher risk for poor neurological outcome compared to patients undergoing craniotomy or who were conservatively treated.
Toussaint 2008	A comprehensive narrative review of the role of decompressive surgery in both TBI and malignant cerebral infarction with a discussion of all important issues still open to debate. Authors included a retrospective analysis of 102 patients with TBI who underwent DC in a 7-year period (2000 to 2007). 6 patients were lost to follow-up, leaving a total of 96 for analysis: 18 pediatric patients and 78 adults. DC was indicated in 25 adults because of neuroradiological signs of diffuse brain swelling or because of refractory high ICP. The mortality rate was 32% (8/25). 32% of patients achieved functional independence. In the pediatric population, 7 patients underwent DC, 2 died, and 3 achieved a functional outcome.

Table 1. Annotated bibliography *(Continued)*

Tsaousi 2018	A systematic review and meta-analysis.Three randomized controlled trials and two observational studies enrolling 3451 patients were selected for qualitative analysis, 4 of which were included in the meta-analysis. Despite the inclusion of observational studies, the conclusions of this review were similar to the present review. The use of DC in TBI patients with intracranial hypertension was associated with survival benefit when compared to medical therapy alone, but with no clear improvement of functional outcome.
Ucar 2005	Prospective, non-randomized single-center study in which unilateral (66 patients) or bilateral (34 patients) DC with duraplasty was performed in patients with high ICP refractory to first-level therapeutic measures. In bilateral decompression, authors preserved a midline bone bridge over the superior sagittal sinus. The main limitation of this study was that 40 of the 66 patients who underwent unilateral DC also had an acute subdural hematoma, 5 had an acute intracerebral hematoma, and 3 extradural hematomas. The volume was not reported in any of these mass lesions. In a secondary analysis of the subgroup who underwent DC with no mass lesion, 80% had an unfavorable outcome according to the dichotomized GOS. The study authors concluded that there was no significant benefit in performing DC in severe head-injury patients with GCS scores of ≤ 5. However, the design of the study did not allow the extraction of such a conclusion.
Venes 1975	Retrospective analysis of 13 moderately and severely head-injured patients with no evidence of mass lesions who underwent bifrontal-bitemporal DC and duraplasty with a pericranium or fascial graft.
Whitfield 1995	Single case report of a successful bifrontal DC in a 13-year old girl with a diffuse bilateral brain swelling.
Whitfield 2001a; Whitfield 2001b	Observational retrospective study of a consecutive series of 26 patients with moderate or severe head injuries who underwent bifrontal DC for the management of refractory raised ICP, between 1992 and 1999. 6 patients were > 16 years of age. Patients were managed according to a strict therapeutic protocol. The ICP threshold used in this study was 30 mmHg to 35 mm Hg depending on CPP. Overall, only 55% of potentially eligible patients underwent craniectomy during the study period. Clinical outcome was categorized using the GOS at least 6 months after surgery. When all patients in the series were taken into consideration, DC significantly reduced ICP from 37.5 mmHg ± 10.0 mmHg to 18.1 mmHg ± 16 mmHg (P = 0.003). In most patients, the reduction in ICP was sustained. In this study, very comprehensive data from pre- and postoperative ICP monitoring was analyzed in 8 patients to evaluate the physiological effects of surgery on ICP. Decompressive bifrontal craniectomy significantly reduced the: • amplitude of the ICP waveform; • amplitude of slow waves; and • compliance of the intracranial space.
Wick 1999	Narrative review including a description of 2 patients with an acute subdural hematoma who underwent primary decompressive hemicraniectomy.
Wettervik 2018	Retrospective study reviewing the usage of both P-DC and (secondary) DC and the long-term outcome of both procedures in a single centre in Upsala (Sweden) between 2008 and 2014.
Winter 2005	A narrative review remarking that literature provided several reports of improvement in patient outcomes following DC for refractory intracranial hypertension. The authors emphasized that although the operation was being used more, current opinion was still divided regarding the overall benefits.
Woldag 2006	Retrospective study published in German in which the functional outcome of 65 patients was assessed. Of these, 41 underwent DC because of stroke and 24 because of TBI.
Xiong 2001	A single-center retrospective study of 218 patients who underwent DC.

Table 1. Annotated bibliography *(Continued)*

Yamakami 1993	Prospective study of 5 patients who underwent unilateral DC. The main goal of the study was to analyze the pattern of regional cerebral blood flow after decompression.
Yamaura 1979	A series of 207 patients who underwent large uni- or bilateral decompressive craniectomies. The decision for surgery was taken exclusively on the basis of clinical criteria (progressive neurological deterioration). No angiographic studies were used when making the decision to decompress. The first series of 154 patients were operated on between 1966 and 1974, while the second series (53 patients) were operated on in 1975 and 1976.
Yang 2003	Retrospective study performed in a rehabilitation center that included 68 patients who underwent external decompression after TBI; in various centers.
Young 2017	Narrative review focused on the indications of S-DC in children. In this review, the as-yet unpublished results of RESCUEicp 2016 in children are commented on (Young 2017, p 1748). According to the authors, of the 408 patients randomised, 56 were ≤18 years and 16 patients were ≤16. The primary analysis showed a significant between-group difference in the extended Glasgow Outcome Scale (GOS-E) distribution and a substantial reduction in mortality with surgery. With the same dichotomization used in adults at 12 months, 45.4% of the patients in the DC group were at least independent at home, as compared with only 32.4% of patients in the medical group (p = 0.01). Authors estimated that treating 100 patients with craniectomy as opposed to medical treatment would result in 22 more survivors of whom, at 12 months, almost 60% will be at least independent at home.
Yue 2019	Narrative review summarizing the indications risks and complications of DC. The two large randomized controlled trials in severe TBI (DECRA 2011 and RESCUEicp 2016) are discussed.
Zhang 2017	A systematic review and meta-analysis to examine the prognostic value of decompressive craniectomy (DC) in patients with traumatic intracranial hypertension. Randomized and non-randomized studies were included. Ten studies were included with 4 RCTs. Apart from the 3 studies included by the authors of this review, Qiu 2009 was also included. We excluded Qiu 2009 for reasons detailed in the table of Excluded studies. The conclusions of this review were that DC was effective to lower ICP and reduce mortality. However, DC increased the incidence of complications, without havinng a clear benefit on functional outcome.
Ziai 2003	A single-center observational study of 18 patients who underwent DC because of a wide variety of intracranial processes: acute hemispheric infarction in 12 patients, TBI in 3, spontaneous intracerebral hemorrhage in 2, and subdural empyema in 1.

CI: confidence interval
CPP: cerebral perfusion pressure
CRASH: Corticosteroid Randomization After Significant Head Injury (trial name)
CT: computed tomography
DC: decompressive craniectomy (secondary)
EEG: electroencephalogram
GCS: Glasgow Coma Scale
GOS: Glasgow Outcome Scale
ICP: intracranial pressure
P-DC: primary decompressive craniectomy
RR: relative risk (risk ratio)
S-DC: secondary decompressive craniectomy
TBI: traumatic brain injury

Table 2. Adverse events/complications

DECRA	Decompressive craniectomy (n = 73)	Medical treatment (n = 82)

Table 2. Adverse events/complications (Continued)

Wound infection or breakdown	5	7
Meningitis or ventriculitis	2	3
Subgaleal infection	2	3
Cerebral abscess	2	0
Cerebrospinal fluid leak	4	2
Hematoma (subgaleal)	5	2
Hematoma (subdural, extradural, or intracerebral)	3	1
Cerebral infarction	1	0
Hydrocephalus	7	1
Cranioplasty revision for cosmetic defect	2	0
Pulmonary embolus	1	2
Pneumonia	0	3
Septic shock	1	2
Acute renal failure	1	1
RESCUEicp	**Decompressive craniectomy (n = 202)**	**Medical treatment (n = 196)**
Acute kidney injury	0	1
Acute respiratory distress syndrome	0	2
Arrhythmia	1	1
Bleeding (surgical complication)	4	0
Bleeding (surgical complication; led to death)	1	0
Cardiac arrest	1	
Cardiogenic shock	0	1
Cerebral infarction	2	2
Deep venous thrombosis	0	1
Diabetes insipidus	0	1
Disseminated intravascular coagulation	1	0
Hydrocephalus	0	1

Table 2. Adverse events/complications *(Continued)*

Hypotension	0	2
Intraoperative respiratory failure	2	0
Liver failure	1	0
Multiple organ dysfunction syndrome	0	1
Myocardial infarction	2	0
Pneumonia	4	6
Postoperative hematoma	5	0
Pulmonary embolism	0	1
Seizures	0	1
Sepsis (not otherwise specified)	1	2
Shock (not otherwise specified)	1	2
Subdural collection	1	1
Subgaleal collection	3	1
Surgical site infection	5	1
Venous sinus injury	1	0
Ventriculostomy/CSF infection	1	2

Authors of the RESCUEicp study reported: "A total number of 37 complications and adverse events were reported in 33 patients of the surgical group. A total number of 32 complications and adverse events were reported in 18 patients of the medical group" (*NEJM Supplement*, Table S10)

Abbreviation
CSF: cerebrospinal fluid

APPENDICES

Appendix 1. Neurological outcome categories according to divisions of the GOS or GOS-E

The traditional Glasgow Outcome Score (GOS) applies to people with brain damage and aims to assess recovery in five categories.

Initially, the cut-off for 'unfavorable' or 'bad' outcome compared to 'favorable' or good' outcome fell between categories 3 and 4; that is, a 'good' outcome meant 'moderate' or 'low' disability only.

1. Death	Severe injury or death without recovery of consciousness
2. Persistent vegetative state	Severe damage with prolonged state of unresponsiveness and a lack of higher mental functions
3. Severe disability	Severe injury with permanent need for help with daily living

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(Continued)

4. Moderate disability	No need for assistance in everyday life, employment is possible but may require special equipment.
5. Low disability	Light damage with minor neurological and psychological deficits.

Later the GOS-E (Extended GOS) raised the number of categories from five to eight, and the cut-off now conventionally falls between categories 4 and 5; i.e. a 'good' outcome ranges from 'upper severe disability' to 'upper good recovery. This was challenged by some in the field, and investigators have also chosen to dichotomize between categories 3 and 4.

1. Dead	
2. Vegetative state	Condition of unawareness with reflex responses only, but with periods of spontaneous eye opening.
3. Low severe disability	Person who is dependent for daily support for mental or physical disability, usually a combination of both. If the person cannot be left alone for more than 8 h at home, it is low level of severe disability.
4. Upper severe disability	Person who is dependent for daily support for mental or physical disability, usually a combination of both. If the person can be left alone for more than 8 h at home, it is upper level of severe disability.
5. Low moderate disability	Person has some disability such as aphasia, hemiparesis or epilepsy and/or deficits of memory or personality but is able to look after him/herself. Person is independent at home but dependent outside. If unable to return to work, even with special arrangements, it is low level of moderate disability.
6.Upper moderate disability	Person has some disability such as aphasia, hemiparesis or epilepsy and/or deficits of memory or personality, but is able to look after him/herself. Person is independent at home, but dependent outside. If able to return to work with special arrangements, it is upper level of moderate disability.
7. Low good recovery	Resumption of normal life with the capacity to work even if pre-injury status has not been achieved. Some people have minor neurological or psychological deficits. If these deficits are disabling, then it is lower level of good recovery.
8. Upper good recovery	Resumption of normal life with the capacity to work even if pre-injury status has not been achieved. Some people have minor neurological or psychological deficits. If these deficits are not disabling then it is upper level of good recovery.

Appendix 2. Neurological outcomes as reported in this review

Range of definitions of 'unfavorable' outcomes			
1.1 Mortality	1.2.1 GOS Cut-off: Death/ vegetative state vs other outcomes	1.2.2 GOS/GOSE cutoff as per RESCUE-icp 2016	1.2.3 Traditional GOS/GOSE cutoff
Death	Death	Death	Death
	Vegetative state	Vegetative state	Vegetative state

(Continued)

	Severe (GOS)/lower severe disability (GOS-E)	Severe (GOS)/lower severe disability (GOS-E)
		Severe (GOS/upper severe disability (GOS-E)

Appendix 3. Search strategies

Injuries Group Specialised Register

#1 ((brain or crani* or surgery or surgical*) AND (decompres*)) AND (INREGISTER) [REFERENCE] [STANDARD]

Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library)

#1MeSH descriptor: [Craniocerebral Trauma] explode all trees
#2MeSH descriptor: [Brain Edema] explode all trees
#3MeSH descriptor: [Glasgow Coma Scale] explode all trees
#4MeSH descriptor: [Glasgow Outcome Scale] explode all trees
#5MeSH descriptor: [Unconsciousness] explode all trees
#6MeSH descriptor: [Cerebrovascular Trauma] explode all trees
#7((head or crani* or cerebr* or capitis or brain* or forebrain* or skull* or hemispher* or intra?cran* or inter?cran* or intracran* or intercran*) near/3 (injur* or trauma* or damag* or wound* * or contusion* or fracture*))
#8((head or crani* or cerebr* or brain* or intra?cran* or inter?cran* or intracran* or intercran*) near/3 (haematoma* or hematoma* or haemorrhag* or hemorrhag* or bleed* or pressur*))
#9(Glasgow near/3 (coma or outcome) near/3 (scale* or score*))
#10"rancho los amigos scale"
#11("diffuse axonal injury" or "diffuse axonal injuries")
#12((brain or cerebral or intracranial) near/3 (oedema or edema or swell*))
#13Unconscious* or coma* or concuss* or 'persistent vegetative state':ti,ab,kw (Word variations have been searched)
#14#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13
#15MeSH descriptor: [Decompression] explode all trees
#16(decompres*) near/3 (brain or crani* or surg*):ti,ab,kw (Word variations have been searched)
#17decompression:ti,ab,kw (Word variations have been searched)
#18#15 or #16 or #17
#19#14 and #18

Ovid MEDLINE(R), Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid OLDMEDLINE(R)

1. exp CRANIOCEREBRAL TRAUMA/
2. exp Cerebrovascular Trauma/
3. exp BRAIN EDEMA/
4. ((brain or cerebral or intracranial) adj3 (oedema or edema or swell$)).ab,ti.
5. exp GLASGOW COMA SCALE/
6. exp GLASGOW OUTCOME SCALE/
7. exp UNCONSCIOUSNESS/
8. (Glasgow adj3 (coma or outcome) adj3 (scale$ or score$)).ab,ti.
9. (Unconscious$ or coma$ or concuss$ or 'persistent vegetative state').ab,ti.
10. "Rancho Los Amigos Scale".ab,ti.
11. ((head or crani$ or cerebr$ or capitis or brain$ or forebrain$ or skull$ or hemispher$ or intra-cran$ or inter-cran$) adj3 (injur$ or trauma$ or damag$ or wound$ or fracture$ or contusion$)).ab,ti.
12. "Diffuse axonal injur$".ab,ti.
13. ((head or crani$ or cerebr$ or brain$ or intra-cran$ or inter-cran$) adj3 (haematoma$ or hematoma$ or haemorrhag$ or hemorrhag$ or bleed$ or pressure)).ab,ti.
14. or/1-13
15. exp Decompression, Surgical/
16. (decompres$ adj3 (brain or crani$ or surg$)).mp.
17. decompression.ti,ab.
18. or/15-17
19. 14 and 18
20. randomi?ed.ab,ti.

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21. randomized controlled trial.pt.
22. controlled clinical trial.pt.
23. placebo.ab.
24. clinical trials as topic.sh.
25. randomly.ab.
26. trial.ti.
27. Comparative Study/
28. 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27
29. (animals not (humans and animals)).sh.
30. 28 not 29
31. 19 and 30

Embase Classic+Embase (OvidSP)

1.exp Brain Injury/
2.exp Brain Edema/
3.exp Glasgow Coma Scale/
4.exp Glasgow Outcome Scale/
5.exp Rancho Los Amigos Scale/
6.exp Unconsciousness/
7.((brain or cerebral or intracranial) adj3 (oedema or edema or swell$)).ab,ti.
8.((head or crani$ or cerebr$ or capitis or brain$ or forebrain$ or skull$ or hemispher$ or intra-cran$ or inter-cran$) adj3 (injur$ or trauma$ or damag$ or wound$ or fracture$ or contusion$)).ab,ti.
9.(Glasgow adj3 (coma or outcome) adj3 (scale$ or score$)).ab,ti.
10.Rancho Los Amigos Scale.ab,ti.
11.(Unconscious$ or coma$ or concuss$ or 'persistent vegetative state').ab,ti.
12.Diffuse axonal injur$.ab,ti.
13.((head or crani$ or cerebr$ or brain$ or intra-cran$ or inter-cran$) adj3 (haematoma$ or hematoma$ or haemorrhag$ or hemorrhag$ or bleed$ or pressure)).ab,ti.
14.or/1-13
15.exp decompression surgery/
16.(decompres$ adj3 (brain or crani$ or surg$)).mp.
17.decompression.ti,ab.
18.15 or 16 or 17
19.14 and 18
20.exp Randomized Controlled Trial/
21.exp controlled clinical trial/
22.randomi?ed.ab,ti.
23.placebo.ab.
24.*Clinical Trial/
25.randomly.ab.
26.trial.ti.
27.20 or 21 or 22 or 23 or 24 or 25 or 26
28.exp animal/ not (exp human/ and exp animal/)
29.27 not 28
30.19 and 29

WEB OF SCIENCE . SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI

#1TS=((singl* OR doubl* OR trebl* OR tripl*) SAME (blind* OR mask*))
#2TS=(randomised OR randomized OR randomly OR random order OR random sequence OR random allocation OR randomly allocated OR at random OR randomized controlled trial) OR TS=(controlled clinical trial OR controlled trial OR clinical trial OR placebo)
#3#1 or #2
#4TS=(human*)
#5#3 and #4
#6TS=((decompres*) same (brain or crani* or surg*)) OR TS=(decompression)
#7TS=((head or crani* or cerebr* or capitis or brain* or forebrain* or skull* or hemispher* or intra-cran* or inter-cran*) same (injur* or trauma* or damag* or wound* or fracture* or contusion*)) OR TS=((head or crani* or cerebr* or brain* or intra-cran* or inter-cran*) same (haematoma* or hematoma* or haemorrhag* or hemorrhag* or bleed* or pressur*))
#8#6 and #7
#9#5 and #8

Trials registries

Condition: Traumatic brain injury
Intervention: Decompressive craniectomy

Appendix 4. Search methods differences between previous versions and this update

For this recent update it was decided not to search CINAHL as it has not contributed references that were useful to the review.

CINAHL (EBSCO) (1982 to May 2011)

1.MH decompression surgery
2.TX decompres* AND (brain or crani* or surgery or surgical*)
3.S1 or S2
4.MH head injuries
5.TX (head or cranial or cerebral or brain* or intra-cranial or inter-cranial) AND (injury* OR injuries OR trauma OR damage OR damaged OR wound* OR fracture* OR contusion* or haematoma* or hematoma* or haemorrhag* or hemorrhage* or bleed* or pressure)
6.S4 or S5
7.S3 and S6
8.MH random assignment
9.PT clinical trial
10.TX randomised or randomized or randomly or random order or random sequence or random allocation or randomly allocated or at random
11.S8 or S9 or S10
12.S7 and S11

We now search **ISI WEB OF SCIENCE Core Collection . SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI rather than ISI Web of Science: Science Citation Index Expanded (SCI-EXPANDED); Conference Proceedings Citation Index- Science (CPCI-S)**

WHAT'S NEW

Date	Event	Description
8 December 2019	New citation required and conclusions have changed	The review has been updated. Data from two new studies are included.
8 December 2019	New search has been performed	The results of new searches have been fully incorporated. The authors of the review have changed.

HISTORY

Protocol first published: Issue 1, 2003
Review first published: Issue 1, 2006

Date	Event	Description
18 February 2009	Amended	Assessed as Up-to-date corrected. The search was last conducted 29 May 2008.
29 May 2008	New search has been performed	May 2008 New studies found and included or excluded.
22 March 2007	Amended	March 2007 In light of a comment posted on the CDSR online feedback system, recommendation 8 in the 'implications for research' section has been revised.

CONTRIBUTIONS OF AUTHORS

Development of the idea for the review: Juan Sahuquillo (JS). He and earlier co-authors Fuat Arikan (FA) and Javier Ibaňez worked on the protocol.

For the first version of the review, JS identified studies, carried out assessment of risk of bias, extracted data, and wrote the full review. He also contacted the principal investigators of ongoing studies to update development and wrote to experts in the field of traumatic brain injury to request feedback. FA conducted the handsearching and contributed to writing the discussion and conclusions.

For the present version of the review, JS and Jane Dennis (JD) identified studies, carried out assessment of risk of bias, extracted data, reorganized and added data to comply with MECIR standards, and added Summary of Findings. JS is responsible for the Discussion and Conclusions.

DECLARATIONS OF INTEREST

JS: has participated in the RESCUEicp 2016 trial. JS was the co-ordinator for the Spanish branch of this trial and enrolled participants. No honoraria or financial gains have or will be obtained by the review author from this clinical trial.
JD: was employed by the Cochrane Injuries for most of the period during which she contributed to this review.

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Internal sources

- London School of Hygiene & Tropical Medicine, UK.

  J Dennis received payment from the Cochrane Injuries Group during the completion of this review. The Cochrane Injuries Group is based at LSHTM.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

- The title of the review has been changed from "Decompressive craniectomy for the treatment of refractory high intracranial pressure in traumatic brain injury" to "Decompressive craniectomy for the treatment of high intracranial pressure in closed traumatic brain injury." This change was made to accommodate some new indications for decompressive craniectomy (DC) found in the literature, in which patients with traumatic brain injury (TBI), high intracranial pressure (ICP) - but not necessarily 'refractory' ICP - were managed with DC.
- The term 'closed TBI' has been introduced in the title because the review is focused only on closed TBI and not the multiple forms of penetrating injuries that occur in military and civilian populations involved in assaults, wars, and armed conflicts.
- We have included all patients with TBI regardless of severity as long as they received ICP monitoring; therefore, patients with a moderate or severe TBI could be eligible for this review.
- Methods decisions have been updated (and Review Manager 5 headings added) to comply with contemporary requirements of the *Cochrane Handbook for Systematic Reviews of Interventions* and for MECIR and GRADE.
- The method of reporting successful management of ICP has been changed from the 2002 protocol (Sahuquillo 2002b) in which it was planned to consider a reduction of 10 mmHg as being significant, to 5 mmHg.
- In the original protocol we made plans to analyze continuous data by dichotomizing ICP control. We found that ICP control was evaluated with different and non-comparable methods in the three included studies (i.e. hourly ICP, different intracranial hypertension indexes, the percentage of time ICP was above a threshold, etc.). Thus, for this version of the review we decided that analysis of ICP data would be summarized best in the form of means and standard deviations (SDs) (where available), with 95% CI.
- In this review, we have also added the absolute risk reduction (ARR) and the number needed to treat for an additional beneficial outcome (NNTB), that is, to avoid the outcome of interest. For calculating ARR and NNBT we have used the online calculator available at (ebm-tools.knowledgetranslation.net/calculator/prospective). We planned at protocol stage that if Glasgow Outcome Scale (GOS) scores were not available, patients in the category of a 'bad' outcome would include those who were dependent for activities of daily living, remained in a vegetative state, and who died. We continued to do so despite the presentation of data in one included study, RESCUEicp 2016, which used a less traditional dichotomization that involved grouping those with 'upper severe disability' into the category of 'good outcome'. In addition to the good/bad outcome analysis described in the original protocol, and because this is an arbitrary dichotomization that generates controversies, we have conducted a new analysis including death/vegetative versus other outcomes. We believe that death and survival in a vegetative status are considered 'bad' outcomes, without generating controversy (Honeybul 2017). This way, the interpretation of the results is easier for clinicians, and stands apart from of the controversy at which particular point of the extended GOS the threshold should be placed to define a 'bad-unfavorable' or 'good-favorable' outcome. In the

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opinion of many, the cut-off to define bad and good outcomes is an arbitrary threshold, the definition of which should be left to the patients and caregivers and not to the health providers.

- A second author (JD) has been added to comply with good practice and to ensure independence regarding extraction and assessment of data from the RESCUEicp 2016 trial in which the lead review author was involved.

I N D E X   T E R M S

Medical Subject Headings (MeSH)

Brain Injuries [*complications]; Craniotomy [*methods]; Decompression, Surgical [*methods]; Intracranial Hypertension [*surgery]; Intracranial Pressure; Randomized Controlled Trials as Topic

MeSH check words

Humans