Article published online: 2022-09-09

Review Article

The Role of Decompressive Craniectomy in Traumatic Brain Injury: A Systematic Review and Meta-analysis

Abstract

The objective is to evaluate the efficacy of early decompressive craniectomy (DC) versus standard medical management ± late DC in improving clinical outcome in patients with traumatic brain injury (TBI). Electronic databases and gray literature (unpublished articles) were searched under different MeSH terms from 1990 to present. Randomized control trials, case–control studies, and prospective cohort studies on DC in moderate and severe TBI. Clinical outcome measures included Glasgow Coma Outcome Scale (GCOS) and extended GCOS, and mortality. Data were extracted to Review Manager software. A total of 45 articles and abstracts that met the inclusion criteria were retrieved and analyzed. Ultimately, seven studies were included in our meta-analysis, which revealed that patients who had early DC had no statistically significant likelihood of having a favorable outcome at 6 months than those who had a standard medical care alone or with late DC (OR of favorable clinical outcome at 6 months: 1.00; 95% confidence interval (CI): 0.75–1.34; $P = 0.99$). The relative risk (RR) of mortality in early DC versus the standard medical care ± late DC at discharge or 6 months is 0.62; 95% CI: 0.40–0.94; $P = 0.03$. Subgroup analysis based on RR of mortality shows that the rate of mortality is reduced significantly in the early DC group as compared to the late DC. RR of Mortality is 0.43; 95% CI: 0.26–0.71; $P = 0.0009$. However, good clinical outcome is the same. Early DC saves lives in patients with TBI. However, further clinical trials are required to prove if early DC improve clinical outcome and to define the best early time frame in performing early DC in TBI population.

Keywords: *Clinical outcome, decompressive craniectomy, traumatic brain injury*

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Introduction

Cerebral edema remains one of the main complications of traumatic brain injury (TBI) that lead to increase in intracranial pressure (ICP) and reduction in the cerebral perfusion pressure (CPP).[1] This would successively cause detrimental effects on the cerebral oxygen metabolism and can lead to catastrophic events.[2-5] In TBI, the cerebral contusion induces the life-threatening brain swelling within the first 2–3 h. The second peak of the brain swelling occurs within 2–5 days due to blood cell breakdown products and activated inflammatory cascades.[6-8]

As per the European Brain Injury Consortium and the American Brain Injury Consortium guidelines for severe TBI, decompressive craniectomy (DC) is one of the therapeutic options when conventional treatment fails to reduce the ICP, which involves; head elevation, sedation, analgesia, and neuromuscular paralysis.[9-17] Other treatment options for treating brain edema includes ventriculostomy (if an external ventricular drain had not already been inserted for ICP monitoring), pharmacologic blood-pressure augmentation, osmotherapy, moderate hypocapnia ($PaCO_2$, 4.0–4.5 kPa [30–34 mmHg]), and therapeutic hypothermia (not <34°C).[18]

DC is a surgical technique designed to provide instantaneous and definitive relief of elevated ICP, especially when there is either unilateral or bilateral diffuse cerebral swelling, neurological deficit, dilated and unreactive pupils, failure of medical treatment with persistent ICP >30 mmHg and CPP <45 mmHg.[9,10,18,19] Although some regard it as a last-ditch effort only to be used when more conservative ICP treatment measures have failed as mentioned above. Evidence suggests that early DC may play an optimal care of patients with elevated ICP.[20-22]

How to cite this article: Fatima N, Al Rumaihi G, Shuaib A, Saqqur M. The role of decompressive craniectomy in traumatic brain injury: A systematic review and meta-analysis. Asian J Neurosurg 2019;14:371-81.

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Access this article online

Website: www.asianjns.org

DOI: 10.4103/ajns.AJNS_289_18

Quick Response Code:

Based on that, an urgent DC can be a life-saving procedure by providing the room for the brain to swell, thus reducing the ICP and maintaining the CPP. However, wait-and-see approach is mostly adopted before the craniectomy or craniotomy of lesions evacuation, with evidence of neurological decline or ICP elevation with or without failure of medical management.[23]

Thus, the timing of DC could be very crucial regarding the surgical outcome despite being still debatable to intervene early or late as a second-tier therapy after the initial trial of medical management has failed.

In most of the cases, DC is performed following the protocol of medical treatment of refractory intracranial edema and hypertension as a secondary procedure (secondary DC).[2,8] The timing of the DC (early vs. late) plays an important role as it may change the pathophysiological responses.[7,8] It has been reported that the right time of DC can be determined by the clinical follow-up, repeated head computed tomography (CT) scans, and continuous ICP and CPP monitoring.[9,10]

The safety and efficacy of DC as an early or late procedure, following the initial conservative management in TBI, has not been fully established due to limited randomized controlled trials (RCTs), looking at the timing of DC in predicting clinical outcome and the difficulty in performing these types of trials. Further studies are required to determine the timing of the DC surgery to improve the patient's clinical outcome.

Our meta-analysis is a further step to determine the efficacy of early DC versus the standard medical care ± late DC in improving the clinical outcome in TBI. Besides, to determine whether early DC versus late DC after failing the medical management of raised ICP has any role in improving the clinical outcome in TBI. Our *a priori* hypothesis was that early DC improves the clinical outcome of patients with moderate-to-severe TBI as compared to the standard medical care ± late DC.

Methods

Search strategy

We developed PICO question. Does the early DC versus the standard medical care ± late DC improves the clinical outcome in moderate-to-severe TBI? Based on that the following PICO question was obtained:

- Population: Patients with moderate-to-severe TBI
- Intervention: Early DC before the medical management
- Control: Standard medical management ± late DC
- Outcome: Extended Glasgow Coma Outcome Scale (GOS-E) at 6 months, GOS at 6 months.

Early or primary DC was defined as DC done at the time of mass lesion evacuation, and can be performed even without taking measures to reduce the ICP[2,8] while late or secondary DC is defined as DC done to treat the refractory ICP, which according to some studies is >24–48 h.[2,8]

The refractory ICP is defined as the raised ICP >25 mmHg that lasts for ≥15 min, which is not responding to the usual medical management.[17,24] The intervention arm received early DC for the TBI. The control arm receives the standard medical care that involves; head elevation, sedation, analgesia, moderate hypothermia, osmotherapy (mannitol or hypertonic saline), and/or cerebrospinal fluid drainage alone or with the late DC.

We applied stringent inclusion criteria, selecting only RCTs, case–control studies (CCSs) or cohort studies (CS), and patients with moderate and severe with TBI who were candidates for DC and randomized to receive either early DC or standard medical care ± late DC. Case-series and retrospective studies were excluded.

We used the following MeSH headings: DC or ICP or TBI. We did not define any limitation in language. Articles published between 1990 and the present were searched. Two reviewers MS and NF completed all the review process.

The following databases were reviewed: the Cochrane Library, Medline, Embase, Web of Science, Google Scholar, Scopus, and PubMed. In addition, we reviewed the following gray literature: unpublished abstracts from the *American and European Neurotrauma conferences* over the past 10 years.

Data extraction and management

Demographic information, detailed methods, interventions, and outcomes were abstracted from the manuscripts chosen for the review and recorded on a special data form.

The data form included the following:

1. Methods: Design, method of randomization, setting of treatment, blindness of treatment or intervention (or not), withdrawals or patients lost to follow-up, type of analysis (intention to treat analysis), and primary and secondary outcomes

Population: Sample size, inclusion and exclusion criteria, age, gender, CT scan findings (based on the MARSHAL classification), time DC, time to medical management

2. Intervention: Early DC
3. Control: Standard medical management ± late DC
4. Outcome: Reported poor and good long- and short-term outcomes and mortality rate.

Outcome measures: several outcome measures were selected for our meta-analysis:

1. Functional outcomes: GOS-E 0–8: outcomes were dichotomized to favorable (5–8) or poor (1–4) from 6 months to 1 year

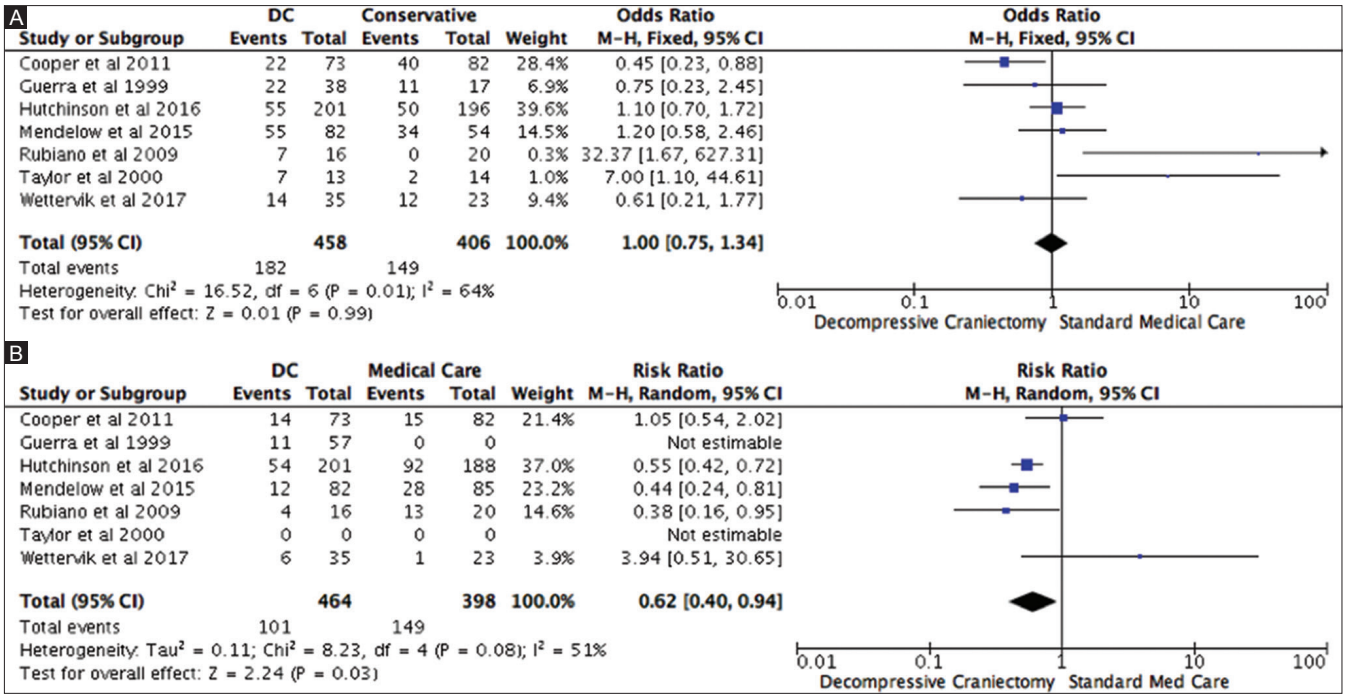

Figure 1: Pooled analysis of all studies: Comparison of decompressive craniectomy versus the standard medical management with or without late decompressive craniectomy. Panel A: The good functional long-term clinical outcome measured by Glasgow Outcome Scale-Extended and Glasgow Outcome Scale at 6 months (6 months; Glasgow Outcome Scale-Extended 4–8, Glasgow Outcome Scale: 4–5) The odds ratio of good clinical outcome was determined using data from all studies. Heterogenity: The probability value corresponds to Breslow–Day Test. Panel B: This figure is indicating the mortality rate at discharge or at 6 months of decompressive craniectomy versus the standard medical care with or without late decompressive craniectomy. The relative risk was calculated based on the data from the above-mentioned studies

2. GOS at 6 months' favorable outcome (4–5) and unfavorable outcome (1–3)
3. Mortality defined as the number of deaths in a particular population per unit of time.

Assessment of risk of bias in included studies

To avoid publication bias, we reviewed the abstracts from the European and American TBI meetings, looking at unpublished trials.

Measures of treatment effect: Treatment efficacy was dichotomized as favorable or poor functional outcome

In order for the DC to be considered effective, we required the threshold between good and poor outcome to be clinically and statistically significant ($P < 0.05$).

Subgroup analysis and investigation of heterogeneity

The following subgroup analysis was performed:

1. Subgroup analysis based on the rate of mortality at discharge or at 6 months of early DC versus medical treatment ± followed by late DC
2. Subgroup analysis based on the rate of mortality at discharge or 6 months of early DC versus the late DC was carried out.
3. Subgroup analysis based on the early DC versus late DC leading to favorable and unfavorable outcome was carried out
4. The pooled meta-analysis was repeated with exclusion of the pediatric trial to measure the effect of early DC in the adult population with moderate-to-severe TBI.

Results

Description of studies

A total of 14,852 titles were reviewed from the above-mentioned electronic literature. Reviewing the gray literature did not add any abstracts. Forty-five studies were retrieved and analyzed. Seven studies (5 RCTs, 1 CCS, and 1 CS) met the inclusion criteria and included in our meta-analysis. The baseline characteristics and safety and efficacy of the RCTs, CCS, and prospective CS are summarized in Tables 1 and 2.

Risk of bias in the randomized control trial studies

None of the RCT trials followed adequate sequence generation (computer generation), and few had the allocation of treatment concealed. Regarding blindness of the investigator and the patient outcome, none of the trials achieved double blindness; some of them achieved single investigator blindness. This is understandable in this type of RCT, in which the procedure is evaluated, and it could be difficult to blind the investigator or the patient to treatment allocation or immediate outcome measure.

Table 1: Baseline characteristics of randomized control trials, case-control studies, and prospective cohort studies

Trial or study	Type of study: RCT/CCS/ Cohort	*n* (treatment/ control)	Intervention (treatment/ control)	Time to craniectomy from randomization	Initial GCS	ICP threshold	Age (intervention/ control) (mean±SD)	Inclusion criteria	Exclusion criteria	Type of injury on the basis of CT scan	Outcome measures
Wettervik *et al.*, 2018[25]	RCT	609:DC: 35 thiopental/no DC group: 23 No thiopental/no DC: 544 Total brain infarction: 7	B/L DC: 6/ hemi-DC: 18 versus medical care (thiopental)	N/A	GCS: 1-2: 5:4:20:5	N/A	40:23:544:7	Same as DECRA and RESCUE-ICP study	Same ad DECRA and RESCUE-ICP study	DI II: 6:6:283:1 DI III: 11:8:67:1 DI IV: 2:1:24:1 Nonevacuated: 0:0:52:3	GOS-E at 6 months
Hutchinson *et al.*, 2016[17] RESCUEicp Trial*	RCT	408 T: 202 versus C: 198 (10 excluded)	Secondary DC (unilateral FTP craniectomy or BF craniec)/medical management	2.2 h	GCS 1 or 2: 96/181 versus 85/170 GCS 3-6: 85/181 versus 85/170	>25 mmHg for 30 min to 1 h	10-65 years 32.3±13.2 versus 34.8±13.7	Head injury requiring ICP monitoring Age 10-65 years Abnormal CT scan Patients may have had an immediate operation for a mass lesion but not a decompressive craniectomy	Bilateral fixed and dilated pupil Bleeding diathesis Injury deemed to be unsurvivable	Diffuse injury: 161/198 versus 141/186 Mass lesion 37/198 versus 45/186	Primary: GOS-E at 6 months Secondary outcomes GOS-E at 12 and 24 months Quality of life SF-36 in adults and SF-10 in children at 6, 12, and 24 months GCS at discharge ICP assessment Time in ICU Time to discharge Economic evaluation

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Table 1: Contd...

Trial or study	Type of study: RCT/CCS/ Cohort	*n* (treatment/ control)	Intervention (treatment/ control)	Time to craniectomy from randomization	Initial GCS	ICP threshold	Age (intervention/ control) (mean±SD)	Inclusion criteria	Exclusion criteria	Type of injury on the basis of CT scan	Outcome measures
Mendelow *et al.*, 2015[26] (STITCH TRAUMA)	RCT	170 patients: 82 versus 86 (2 excluded)	Early surgery versus medicaltreatment	Mean 4 versus 58	13-15; 70 9-12; 71 8 or less; 27	>30 mmHg	51 (32-63) versus 50 (33-61)	TBI within 48 h of injury No more than 2 Intraparenchymal hemorrhages of 10 ml or more	Extradural or subdural hematoma that required surgery Three or more separate hematoma cerebellar hemorrhage/ contusion Surgery could not be performed within 12 h of randomization Preexisting physical or mental disability	Evidence of TICH on CT scan with a confluent volume of attenuation	Primary outcome: GOS at 6 months Secondary outcomes GOS-E Rankin Eurpeon quality of life-5 dimension scale (EQ-5D) at 6 months
Cooper *et al.*, 2011[24] DECRA Trial***	RCT	165: T: 73 versus C: 82	BFT craniectomy versus standard care	2.3 h	5 versus 6	>20 mmHg for 1-2 h	23.7 years versus 24.6 years	Ages of 15-59 years Severe, nonpenetrating TBI GCS 3-8 Marshal Class 3 on CT scan	Not deemed suitable for full active treatment dilated, unreactive pupils, mass lesions, spinal cord injury, and cardiac arrest	Diffuse injury II 17 versus 27 Diffuse injury III or IV 53 versus 53 Nonevacuated mass lesion VI 3 versus 2	Primary outcome: GOS-E at 6 months Secondary outcome ICP hourly Intracranial hypertension index Number of days in the hospital and ICU

Contd...

Table 1: Contd...

Trial or study	Type of study: RCT/CCS/ Cohort	*n* (treatment/ control)	Intervention (treatment/ control)	Time to craniectomy from randomization	Initial GCS	ICP threshold	Age (intervention/ control) (mean±SD)	Inclusion criteria	Exclusion criteria	Type of injury on the basis of CT scan	Outcome measures
											Mortality in the hospital and at 6 months The proportion of survivors with a score of 2-4
Rubiano *et al.*, 2009[27]	Case-control study	T: 16 C: 20	Primary decompression versus secondary decompression as a second tier therapy	Within 12 h of early decompression while 24-48 h of medical management	Severe head injury GCS <9	25 mmHg	18.3 years versus 24.3 years	Age younger than 50 years GCS <9 after CPR Isolated nonpenetrating head injury Time from injury <12 h Absence of brain death	Brain dead	CT with diffuse injury III or IV of the Marshall classification	Primary outcomes: Mortaliy and Glasgow Coma Outcome Scale Secondary outcomes include Length of stay Total hospital length of stay Discharge status
Taylor *et al.*, 2001[28]	RCT	27: 14 medical versus 13 to DC	Standarized management versus SM+DC	19.2 h (since time of injury) 6 h of randomization	Medical control median GCS of 5 versus intervention median GCS of 6	20 mmHg	Median age 120.9 months	Children over 12 months of age TBI with functioning intraventricular catheter	N/A	Marshall CT criteria	Primary outcome: Glasgow outcome score and healthy state utility index

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Table 1: Contd...

Trial or study	Type of study: RCT/CCS/ Cohort	*n* (treatment/ control)	Intervention (treatment/ control)	Time to craniectomy from randomization	Initial GCS	ICP threshold	Age (intervention/ control) (mean±SD)	Inclusion criteria	Exclusion criteria	Type of injury on the basis of CT scan	Outcome measures
Guerra *et al*., 1999[9]	Prospective Cohort	57 patients: 39 (posttraumatic massive edema; therapy resistant intracranial hypertension) versus 18 (space occupying hematoma)	HC for unilateral edema/swelling versus bilateral decompression over bilateral diffuse edema/ sswelling	Average 4 days postaccident	4 or higher	30 mmHg	1977-1988; younger than 30 1989' younger than 40 years 1991; younger than 50 (except two patients 55 and 66 years)	Appearance of diffuse unilateral or bilateral brain swelling on the CT scan with correlating clinical deterioration Worsening of GCS score and/or dilation of pupils unresponsive to light Therapy-resistant increase in ICP to more than 30 mm Hg and/or a reduction in CPP to <45 mm Hg Initial GCS score of 4 or higher and a GCS score of at least 4 on the 1st posttraumatic day	Patient older than 30 years old Patients with devastating primary brain damage GCS 3 and/ or bilateral fixed, dilated pupils	Diffuse brain swelling 31 patients with unilateral versus 26 patients with bilateral edema	Glasgow Coma Outcome Scale at 12 months

*DECRA Trial – Early decompressive craniectomy in traumatic brain injury; **STITCH – Surgical trial in intracerebral hemorrhage; ***RESCUEicp – Randomized evaluation of surgery with craniectomy for uncontrollable elevation of intracranial pressure. RCT – Randomized controlled trial; DC – Decompressive craniectomy; B/L DC – Bilateral decompressive craniectomy; GCS – Glasgow Coma Scale; DI – Diffuse injury; GOS-E – Extended Glasgow Coma Outcome Scale; GCOS – Glasgow Coma Outcome Scale; TICH – Traumatic intracranial hemorrhage; N/A – Not applicable; ICP – Intracranial pressure; CT – Computed tomography; CPP – Cerebral perfusion pressure; TBI – Traumatic brain injury; BFT – Bifrontal Craniectomy; FTP – Frontotemporoparietal; CPR – Cardiopulmonary resuscitation; BF – Bifrontal

Table 2: Clinical outcomes of randomized control trials, case-control studies, and prospective cohort studies

Trial or study	DC	Medical	6-months GOS-E/GOS	6-months GOS-E/GOS (DC)	6-months GOS-E/GOS (medical)	GCS at discharge	Subgroup analysis: With versus without barbiturate	Mortality at 6 months	Time to discharge
Wettervik *et al*., 2018[25]	18/35 as a secondary DC versus 17/35 as a primary procedure; B/L DC: 6/ Hemi-DC 18/ Bone-flap: 11	23 with thiopental	Unfavorable outcome: 24 versus 12 versus 211 versus 14 Favorable outcome: 14 versus 12 versus 350 versus 7	GOS-E Favorable: 14/35 Unfavorable: 21/35	GOS-E Favorable: 12/23 Unfavorable: 11/23	Dead: 9:2:62:7 Vegetative: 3:2:4:0	Favorable outcome: 4/9 versus 7/26 Unfavorable outcome: 5/9 versus 19/26	6/35 versus 1/23	N/A
Hutchinson *et al*., 2016[17] RESCUEicp Trial	T: 187/202 B/F: 109/173 U/L: 64/173	Barbiturate infusion: 73/196	Unfavorable outcome: 146 versus 136 Favorable outcome: 55 versus 50	GOS-E Favorable: 55/201 Unfavorable: 146/201	Favorable: 50/196 Unfavorable: 138/196	Death: 42/185 versus 83/171	As mentioned previously	54/201 versus 92/188	15 versus 20.8 days
Mendelow *et al*., 2015[26] STITCH Trial	Early surgery: 61 versus 31	21 versus 55	Favorable: 52/82 versus 45/85 Unfavorable: 30/82 versus 40/85	GOS Favorable: 52/82 Unfavorable: 40/82	GOS Favorable: 34/54 Unfavorable: 20/54	Dead: 12 versus 28 Vegetative none	N/A	12/82 versus 28/85	N/A
Cooper *et al*., 2011[24] DECRA Trial	Early DC: 73/155	82/155	Unfavorable outcome: 51 versus 42 Favorable outcome: 22 versus 40	GOS-E Favorable: 22/73 Unfavorable: 51/73	GOS-E Favorable: 40/82 Unfavorable: 42/82	Death: 14 versus 15	GOS-E death 14 versus 15 Vegetative state 9 versus 2	14/73 versus 15/82	28 versus 37 days
Rubiano *et al*., 2009[27]	Early DC: 16/36	20/36	Unfavorable outcome: 5/12 versus 7/13 Favorable outcome: 7/12 versus 0/13	GOS Favorable: 7/16 Unfavorable: 9/16	GOS Favorable: 0/20 Unfavorable: 13/20	Dead 4/16 versus 13/20	N/A	4/16 versus 13/20	23.4 days versus 10.1 days
Taylor *et al*., 2001[28]	DC bitemporal craniectomy: 13/27	14/27	Unfavorable out coma s per GCOS 6 DC versus 12 control Favorable outcome 7 DC versus 2 control	GOS Favorable: 7/13 Unfavorable: 6/13	GOS Favorable: 2/14 Unfavorable: 12/14	Dead 3 DC (withdrawal of treatment) versus 6 (2 brain dead; 3n poor prognosis; 1 cerebral herniation)	Health state utility index at 6 months Unfavorable: 7 versus 13 Favorable: 6 versus 1		N/A
Guerra *et al*., 1999[9]	Early DC: 38/57	Initial conservative: 17/57	Favorable outcome 22 versus 11 Unfavorable outcome 16 versus 6	GOS Favorable: 22/38 Unfavorable: 16/38	GOS Favorable: 11/17 Unfavorable: 6/17	Dead 11 Vegetative 5	N/A	11/57 versus not mentioned	N/A

DC – Decompressive craniectomy; B/L DC – Bilateral decompressive craniectomy; DI – Diffuse injury; GOS-E – Extended Glasgow Coma Outcome Scale; GCS – Glasgow Coma Scale; GOS – Glasgow Coma Outcome Scale; ICP – Intracranial pressure; DECRA Trial – Early decompressive craniectomy in traumatic brain injury; RESCUEicp – Randomized evaluation of surgery with craniectomy for uncontrollable elevation of intracranial pressure; STITCH – Surgical trial in intracerebral hemorrhage; N/A – Not applicable

Effects of interventions

The pooled meta-analysis of all seven studies (treatment arm 458 and control arm 406) revealed the following:

There is no statistically significant difference in the good clinical outcome at 6 months–1 year between early DC and medical treatment with or without late DC (Odds ratio [OR] of favorable clinical outcome at 6 months: 1.00; 95% confidence interval (CI): 0.75–1.34; $P = 0.99$). Hence, there does not exist any comparative difference in the clinical outcome between the intervention and the control arm as indicated in [Figure 1 Panel A].

Six studies have reported the mortality rate in their results.[17,24-29] The RR of mortality at discharge or 6 months is 0.62; 95% CI: 0.40–0.94; $P = 0.03$. Hence, the mortality rate is reduced with the early DC as compared to the standard medical management ± late DC as showed in [Figure 1 Panel B].

The outcome in the adult population after excluding the pediatric population in the first study[28] indicates that OR of favorable clinical outcome at 6 months: 0.94; 95% CI: 0.70–1.27; $P = 0.70$. The RR of mortality at discharge or 6 months is 0.59; 95% CI: 0.47–0.74; $P < 0.00001$.

Only three studies compared the early DC versus the late DC in TBI.[9,26] There is no statistical significance difference in the good clinical outcome and unfavorable clinical outcome among those patients who had early DC versus late DC. The OR of good clinical outcome; 1.30; 95% CI: 0.75–2.27; $P = 0.35$ [Figure 2 Panel A].

Regarding the mortality rate, it is reduced significantly in the early DC group as compared to the late DC group. RR of mortality rate in early DC versus late DC is 0.43; 95% CI: 0.26–0.71; $P = 0.0009$, [Figure 2 Panel B].

Discussion

Our meta-analysis revealed that early DC and standard medical management whether alone or accompanied by late DC has almost the same effect on the functional clinical outcome of the patients with TBI. However, early DC reduces the mortality rate as compared to the patients who underwent late DC. However, because of several limitations in the studies mentioned above (lack of universal outcome scale, no double blindness in randomization, and clinical follow-up, and the small sample size in some studies), future double-blind, randomized control trial with large sample size is needed to prove the concept of early versus late DC. In addition, more evidence is required regarding the timing of the surgery in improving the clinical and functional outcome of patients with TBI.

The medical literature regarding early DC is very conflicting. There are several studies not in support of early DC. For example, Faleiro *et al*.[30] dichotomized 89 patients into <6 h, 6–24 h, and >24 h for DC and found that patients who were operated early had 59% mortality as compared to the 53% of patients who had the surgery later. Al-Jishi *et al*.[31] found that the primary DC had 45.5% good outcome and 40.9% mortality whereas, secondary DC had 73.1% good outcome and 15.4% mortality in his retrospective study. Albanèse *et al*.[32] found that patients who had primary decompression within 24 h had 20% good recovery and 50% died, while those who had secondary decompression (>24 h) had 38% good recovery and only 20% died. An early decompression was performed if the GCS was <6 with clinical signs of cerebral herniation (the absence of pupillary reflexes); ICP was not measured in these patients. The late decompression was performed if patients had intractable intracranial hypertension of >35 mmHg, unilateral or bilateral absence of pupillary reflex with abnormal CT head findings. However, he recommended performing early surgery in patients with intracranial hematoma and brain swelling, which eventually will improve the clinical outcome.

On the other hand, there are some literatures in support of early DC in improving outcome. For example, Honeybul *et al*.[33] carried out a cohort of 186 patients who required DC for severe TBI (2004–2010) indicated that none of the patients improved to achieve a level of independence

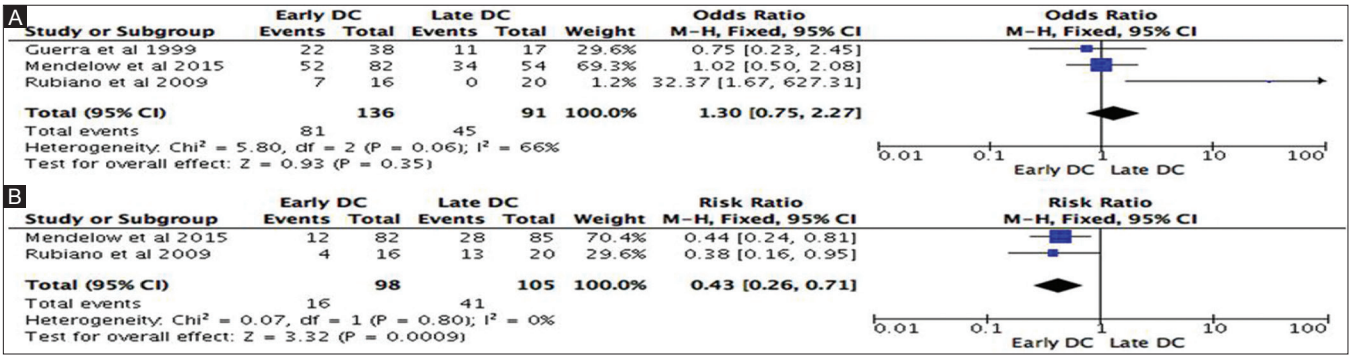

Figure 2: Panel A: Subgroup analysis based upon the favorable clinical outcome: The panel shows favorable clinical outcome at 6 months of early decompressive craniectomy versus the late decompressive craniectomy. The odds ratio of favorable clinical outcome; 1.30; 95% confidence interval: 0.75–2.27; *P* = 0.35. Panel B: Subgroup analysis based on Relative Risk of Mortality: The panel shows mortality of early decompressive craniectomy versus the late decompressive craniectomy. The risk ratio of mortality; 0.43; 95% confidence interval: 0.26–0.71; *P* = 0.0009

or moderate disability, many did appear to have adapted to their disability and recalibrated their expectations for quality of life to a level of disability that they have previously thought unacceptable. Hartings *et al*.[8] compared the neurosurgical approaches in the treatment of TBI at two academic centers in the Cooperative Studies on Brain Injury Depolarizations at Kings College Hospital (KCH, n = 27) and Virginia Commonwealth University (VCU, n = 24) from July 2004 to March 2010. He found that patients treated at VCU underwent surgery earlier, had larger bone flaps, and more frequently underwent craniectomy than craniotomy. These differences were particularly accentuated in patients undergoing earlier lesion evacuation and corresponded to significantly lower postoperative IC*P* values, less spreading depolarizations, and better outcome (good outcome in 69% vs. 29% of cases). As by Seelig *et al*.,[29] if the surgery could be performed within 4 h, the mortality is only 30%, whereas if the surgery is performed over the 4 h, then the rate of mortality increases over 90%. Akyuz *et al*.[34] noted that the 40 patients who had early decompressive surgery as first tiers had much more portion of a better outcome than the other 36 patients operated as second tier (44.4% vs. 12.5%, P = 0.0018).

From the first glance at our meta-analysis result, one might conclude that there is no benefit from early DC in TBI patients. However, the intervention if carried out at an early stage is associated with decrease in the mortality rate. Our meta-analysis finding might be explained by being underpowered to show clinical benefit, and further trials are needed with larger sample size to evaluate the efficacy of early or primary DC versus the late or secondary DC in moderate-to-severe TBI.

Our study has several limitations. First, there is the possibility of selection and publication bias in our systematic review since only two reviewers carried out this part of the process. The reviewers might therefore be more influenced by the positive trial results than by the negative ones. However, we tried to limit such bias by doing the following steps: a gray literature review, in which, we reviewed the abstracts from several meetings to capture any RCT that was presented as an abstract but not published because of a negative result. Second, the lack of access to individual patient's data is one of the limitations. Third, there is a lack of same use of outcome scale among all the studies as some used GCOS while other used Extended Glasgow Coma Scale. Finally, our meta-analysis results cannot be generalized to all forms of decompressive craniectomies as there exists the difference between the thresholds of ICP as well as the timing of DC; thus, the intervention in the form of DC is dependent on it.

In conclusion, our data point that early DC saves life. However, there is no clinically significant relationship in the favorable and unfavorable clinical outcome between the two groups. Thus, our meta-analysis provides a basis to design the RCT with less bias, and determine the sample size of Phase-2 randomized trial of early versus late DC in patients with moderate-to-severe TBI.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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