DECOMPRESSIVE CRANIECTOMY IN THE MANAGEMENT OF NEUROLOGICAL EMERGENCIES

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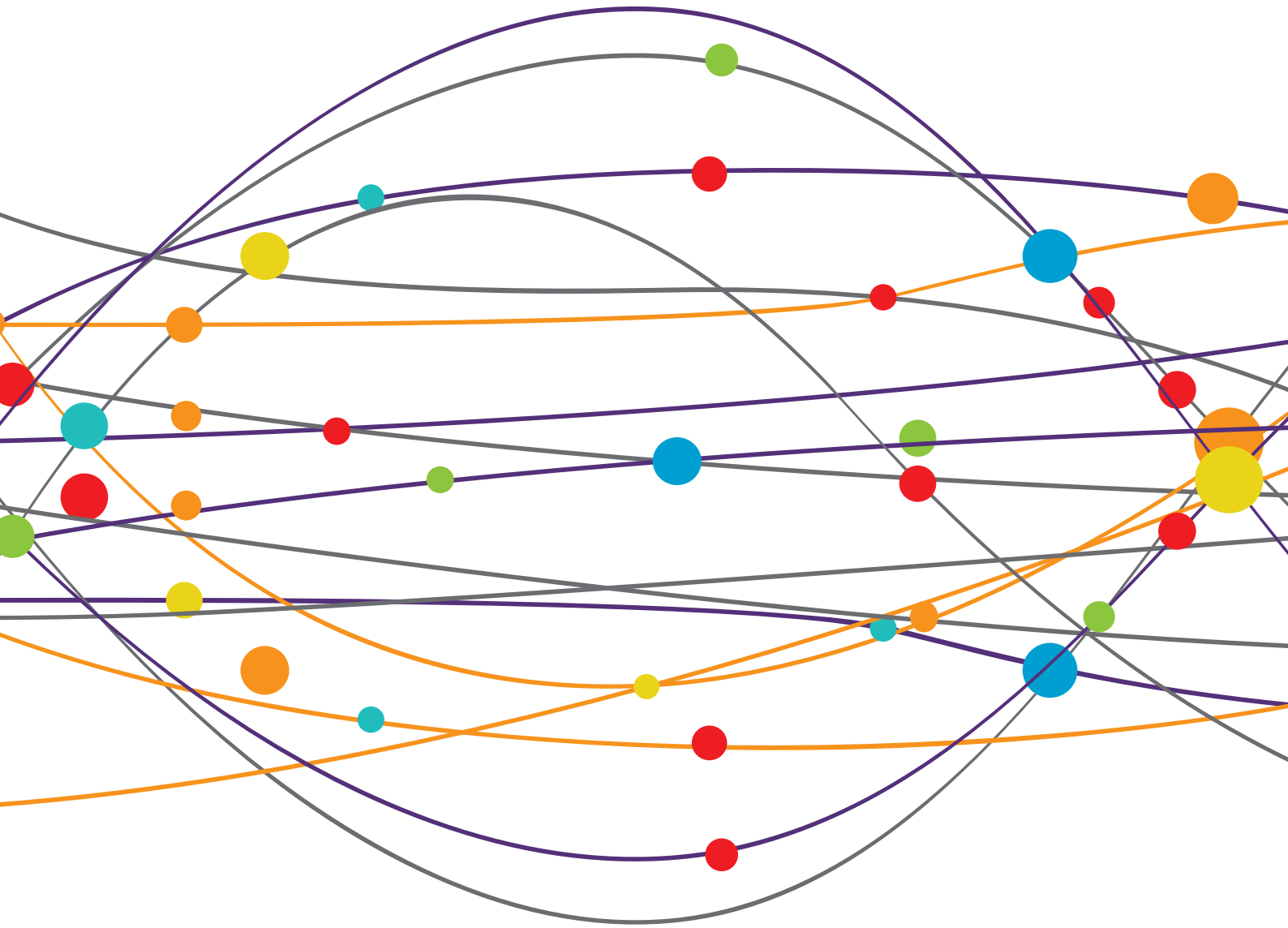

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DECOMPRESSIVE CRANIECTOMY IN THE MANAGEMENT OF NEUROLOGICAL EMERGENCIES

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REVIEW
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Complications of Decompressive Craniectomy

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Decompressive craniectomy (DC) has become the definitive surgical procedure to manage medically intractable rise in intracranial pressure due to stroke and traumatic brain injury. With incoming evidence from recent multi-centric randomized controlled trials to support its use, we could expect a significant rise in the number of patients who undergo this procedure. Although one would argue that the procedure reduces mortality only at the expense of increasing the proportion of the severely disabled, what is not contested is that patients face the risk of a large number of complications after the operation and that can further compromise the quality of life. Decompressive craniectomy (DC), which is designed to overcome the space constraints of the Monro Kellie doctrine, perturbs the cerebral blood, and CSF flow dynamics. Resultant complications occur days to months after the surgical procedure in a time pattern that can be anticipated with advantage in managing them. New or expanding hematomas that occur within the first few days can be life-threatening and we recommend CT scans at 24 and 48 h postoperatively to detect them. Surgeons should also be mindful of the myriad manifestations of peculiar complications like the syndrome of the trephined and neurological deterioration due to paradoxical herniation which may occur many months after the decompression. A sufficiently large frontotemporoparietal craniectomy, 15 cm in diameter, increases the effectiveness of the procedure and reduces chances of external cerebral herniation. An early cranioplasty, as soon as the brain is lax, appears to be a reasonable choice to mitigate many of the late complications. Complications, their causes, consequences, and measures to manage them are described in this chapter.

Keywords: decompressive craniectomy, hemorrhage expansion, infections, cerebral herniation, seizures, hydrocephalus, syndrome of the trephined

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INTRODUCTION

In medicine, there is increasing awareness that outcome must be evaluated in terms of quality of life and cost effectiveness, rather than merely extending the survival of a patient. Such considerations are especially important in decompressive craniectomy (DC), which is performed in certain cases of ischemic stroke, traumatic brain injury, and subarachnoid hemorrhage, to alleviate (ICP) and massive brain swelling (1–3). ICP reduction can lead to improvements in cerebrovascular compliance, cerebral oxygenation, and cerebral perfusion (4). Though many studies have shown long-term beneficial effects after DC (1, 5–7) it is still regarded as a salvage surgery. Long-term, deleterious neurocognitive, and psychosocial effects resulting in poor quality of life, and economical burden are well known (6, 8).

Anticipating a possible rise in the frequency with which decompressive craniectomies are likely to be carried out, based on the strength of recent, strong, supportive, level-one evidence in both traumatic brain injury (9) and stroke (10, 11), complication avoidance should become the new focus in surgical management and research. Currently, there is only low-quality evidence to choose the kind of interventions to avoid complications. Understanding the type and burden of the potential complications, the timeline of their appearance and the reasons why they develop will hold the key to designing good quality randomized controlled trials in the future.

After DC, cranioplasty has to be done (7) using autologous skull, or costly synthetic materials (12). Apart from its own set of complications, cranioplasty creates serious economical burden (13) in low-to-middle income countries (LMICs). They are described in detail in another chapter.

In this chapter, we classify and describe the complications of DC and suggest management techniques that can reduce the risks.

COMPLICATIONS

Decompressive Craniectomy

Decompressive craniectomy has many known complications. The overall complication rates range up to 53.9% (14).

Classification

We suggest that complications be classified as those that occur in the first 4 weeks (early) and those that manifest later (late or delayed). Early complications, which occur in the first 4 weeks, are likely to happen while the patients is still at the hospital. Specific complications tend to occur during particular time periods and awareness of that information helps anticipate and treat them efficiently. Kurland et al. classified them as (i) hemorrhagic, (ii) infectious/inflammatory, and (iii) disturbances of the CSF compartment (15). They tabulated the overall average frequency of each of the complications from a total of 142 eligible reports of thousands of patients who underwent decompressive procedures. They found that one in ten patients who underwent DC develop a complication that required additional medical and/or neurosurgical intervention.

Timeline of Various Complications

Ban et al. reported, from their analysis of 89 patients, that specific complications occurred in a sequential fashion (14). Complications like cerebral contusion expansion (2.2 ± 1.2 days), newly appearing subdural or epidural hematoma contralateral to the craniectomy defect (1.5 ± 0.9 days), epilepsy (2.7 ± 1.5 days), CSF leakage through the scalp incision (7.0 ± 4.2 days), and external cerebral herniation (5.5 ± 3.3 days) occurred early. Subdural effusion (10.8 ± 5.2 days) and postoperative infection (9.8 ± 3.1 days) developed between 1 and 4 weeks postoperatively. Syndrome of the trephined and post-traumatic hydrocephalus developed after 1 month postoperatively (at 79.5 ± 23.6 and 49.2 ± 14.1 days, respectively).

TABLE 1 | Overview of complications associated with decompressive craniectomy.

	Decompressive craniectomy
Early	• Hemorrhage (hematoma expansion) • External cerebral herniation • Wound complications • CSF leak/fistulae • Postoperative infection • Seizures/epilepsy
Late or delayed	• Subdural hygroma • Hydrocephalus • Syndrome of the Trephined

Risk Factors For Developing Complications

Patient-specific risk factors for developing complications include poor neurological status and age. A low preoperative GCS (below eight) has been shown to increase the possibility of all types of complications (16). Age over 65 years is another risk factor (14). Though these risk factors are not modifiable, the surgical team should identify these risk groups to diligently look for emerging complications.

An overview of the complications is provided in **Table 1**, **2** summarizes probable causes, consequences, and management options.

EARLY COMPLICATIONS

Hemorrhage

Expansion of conservatively managed contusions and other bleeds are major issues that occur early after the DC (**Figure 1**). Most expansions occur acutely after surgery and cause clinical deterioration, prolonged hospital stay, and can even prove fatal. One theory is that the hemostatic (or tamponade) effect is lost when removing the bone, and that, along with reduction in ICP facilitates the expansion mostly on the ipsilateral side. (17–19). This hypothesis is supported by the report from Flint et al. where the propensity was higher on the side of the decompression. In their series of 40 patients, new or expanded hemorrhagic contusions were observed in 23 (58%) of 40 patients and 80% of that occurred ipsilaterally (20). Other kinds of hematomas like extradural hematomas and acute subdural hematomas can either appear *de novo* or increase in size. Expansion or evolution of new, remotely located extradural hematomas, typically occur at a fracture site (21). Expansion of hematoma contralateral or remote from the side of the craniectomy has not been commonly reported in stroke patients.

A contralateral hematoma developed an average of 2.1 days after the primary decompression surgery (16) and an ipsilateral one happened after a mean of 1.5 days (14). In the multivariate analysis of the complications in 89 consecutive patients who underwent DC, only contusion expansion led to poor outcome (14). Hemorrhagic progression of infarcts occur at a frequency

TABLE 2 | Types, causes, consequences, and measures to avoid or treat complications.

Types of complications	Causes	Consequences	Measures to avoid or mitigate the complication
Expansion of conservatively managed contusions and appearance of new bleed	Loss of tamponade effect compounding the natural tendency of contusions to progress	Deterioration in sensorium, the need for evacuation	Early and more frequent scans after decompressive craniectomies at 24 and 48 h, especially in patients with contusions and contralateral calvarial fractures
Extracranial cerebral herniation	Brain edema, inadequate size of the craniectomy	Venous compromise at the edge of the craniectomy leading to further bulge and damage	Adequate size of decompressive craniectomy, re-exploration to increase the size of the decompression (rescue decompression), inserting vascular cushion at draining veins
Postoperative epilepsy	Reduced threshold for seizures but not known if the incidence is higher than if the patient has not undergone decompression. Possible effect of stretching of the scar due to sinking scalp flap	Increased metabolic demand, desaturation	Adequate dose of antiepileptic agents, early cranioplasty, as soon as possible (ASAP)
CSF leakage	Brain bulge and inability to perform watertight dural closure	Meningitis	Early detection and resuturing, water tight duraplasty
Subdural effusion	CSF flow abnormality	Usually resolves on its own	The superior and medial margin of the craniotomy should not be closer than 2.5 cm from the midline, early postoperative pressure dressing
Post-traumatic hydrocephalus	CSF flow abnormality	Deterioration, need for CSF diversion	Superior and medial margin of the craniotomy should not be closer than 2.5 cm from the midline; CSF diversion required
Postoperative neurological deterioration due to decompression	Distortion of the white matter tracts	Failure to achieve benefits of decompression	Excessively large decompression
Syndrome of the trephined	Sinking scalp flap due to lack of support and sub-atmospheric pressure causes changes in blood flow and fluid shifts	Multiple new symptoms, delayed deterioration, and failure to hold the gains of initial improvement	Early cranioplasty (ASAP), pull up with external fixator if cranioplasty cannot be done
Postoperative infection	Greater propensity for wound breakdown and CSF leaks	Greater mortality, increase in duration of hospital stay, delay in cranioplasty	Prophylactic antibiotics
Paradoxical herniation	Subatmospheric negative intracranial pressure under the sinking flap and removal of CSF, typically by lumbar puncture.	Deterioration in sensorium and new neurological deficits	Intravenous hydration, Trendelenburg position, blood patch, and early (ASAP) cranioplasty
A higher chance for injury with trivial trauma	Unprotected cranial contents when cranioplasty is delayed	Severe injuries or death	Hinge cranioplasty, early cranioplasty

of about 23.7% (123/519) of malignant stroke patients who underwent DC (15).

We suggest mandatory CT scan(s) in the first 48 h after DC to help detect this complication quickly and limit the damage.

External Cerebral Herniation

External cerebral herniation appears during the first week after surgery (**Figure 2**). Yang defined it as more than 1.5 cm of herniated brain tissue through the center of the craniectomy defect (16). The incidence is up to 25%. It is thought to be caused by the edema induced by cerebral re-perfusion and increased hydrostatic gradient from the capillaries, after decompression (17). Brain edema causes bulging of the brain and kinking of the draining veins at the edges of the craniectomy which in turn causes venous congestion, infarcts, further herniation, and brain parenchymal lacerations (22). Adequately large craniotomies and augmentative duraplasty avoid herniation (14). The Brain Trauma Foundation recommends that a large frontotemporoparietal DC (not less than 12 × 15 or 15 cm diameter) is needed over a small frontotemporoparietal DC for reduced mortality and improved neurologic outcomes in patients with severe TBI (23). Placing two small gelfoam pledgets on either side of drains at the craniectomy may prevent venous occlusion.

Paradoxical herniation is an unusual complication that tends to occur when there is negative, sub-atmospheric intracranial pressure under the caved-in scalp flap causing the brain to herniate when procedures like lumbar puncture CSF removal (24), ventriculoperitoneal shunt, subdural fluid drainage (25), or even making the patient assume a vertical position for postoperative mobilization is done (26). Intravenous hydration and Trendelenburg position has been used to successfully reverse the herniation.

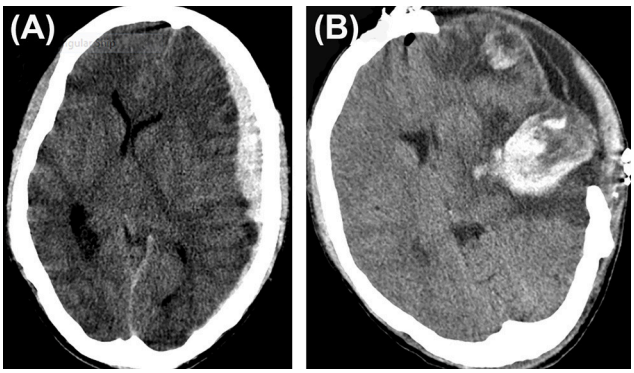

FIGURE 1 | Hematoma expansion. **(A)** A case of traumatic brain injury depicting subdural hematoma **(B)**, hematoma expansion, and subdural collection post craniectomy.

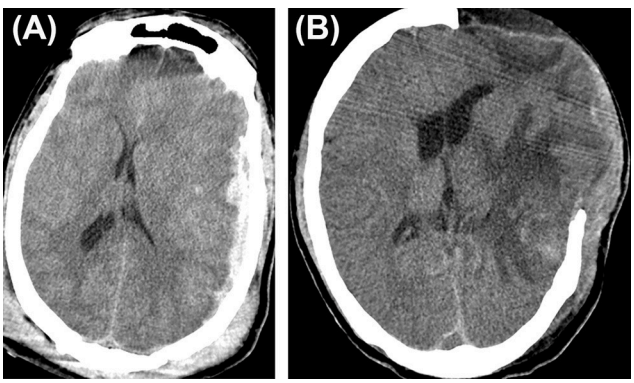

FIGURE 2 | Cerebral herniation. **(A)** A case of traumatic brain injury depicting cerebral herniation **(B)** from the craniectomy site.

Wound Complications

Wound complications following DC or cranioplasty after DC have been classified as dehiscence, ulceration, or necrosis (27). The large size of the scalp flap and the increased probability of injury to the superficial temporal artery during emergency surgery predispose the wound edges to ischemia at the posterior parietal and temporal areas. The pressure of the brain bulge aggravates the ischemia. The underlying, exposed, injured, or ischemic brain is especially vulnerable to infective complications once the wound breaks down.

Meticulously preserving the superficial temporal artery and limiting the posterior extent of the flap to no more than 5 cm behind the ear could reduce chance of ischemic flap breakdown. A retrospective comparison of patients operated using an n-shaped incision with those who were operated using the conventional question mark flap showed that the former technique could accomplish greater bony decompression, allows more brain protrusion and is faster to perform (28). We have noticed that making a retroauricular incision could also reduce flap necrosis.

CSF Leak/Fistulae

The overall prevalence of CSF leak/fistulae due to DC has been shown to be up to 6.3% (15). In patients undergoing DC for cerebral venous sinus thrombosis (CVST), it was seen in 2.9% (29). It appears intuitive that a meticulous augmentative duraplasty and watertight scalp closure would prevent the exodus of CSF from the wound and reduce infection risk. However, a recent randomized controlled trial where watertight duraplasty was compared with rapid-closure DC without watertight duraplasty, there was no statistically significant difference in complications like CSF leak between the two groups of 29 patients each (30). Rapid closure DC without water tight duraplasty was on an average 31 min faster and hence cheaper. Though the authors claim that both procedures are equivalent, the trial was never powered or designed to prove non-inferiority of the test procedure and hence the results should be taken with caution (31).

Postoperative Infections

Superficial wound infections including wound breakdown, necrosis, surgical site infection, sub-galeal collections, and wound breakdown occurred in about 10% of patients and incidence of deeper infections like an epidural abscess, and subdural empyema was just under 4% (15). **Figure 3** shows a brain abscess which developed 2 months after DC for CVST (**Figure 3C**).

The incidence of meningitis and ventriculitis is 4% probably due to the higher chances of CSF leaks. Early detection by looking for signs of meningeal irritation and guarded lumbar puncture CSF analysis is warranted.

Apart from the scalp wound complications, wound breakdown, and infection can occur when the bone flap is preserved in an abdominal pouch (**Figure 4**).

Seizures/Epilepsy

Postoperative epilepsy has been documented in a varying proportion of patients who have undergone DC (14, 32–36). Suggested mechanisms include graded increases in hyperexcitability and a reduced epileptogenic threshold (14, 37). Creutzfeldt et al. retrospectively assessed 55 patients who underwent DC for malignant middle cerebral artery infarction. Of these, 49% of the patients developed seizures within the first week and 45% developed epilepsy within 1 year of surgery (32). Similarly, Santamarina et al. observed occurrence of seizures in 47.5% of all patients and in 53.7% of survivors undergoing DC for malignant MCA infarction. Logistic regression revealed that only prolonged delay from the onset of stroke to decompression (>42 h) independently predicted the development of epilepsy (34). In another study, Brondani et al. reported the prevalence of seizures in 61% (21 out of 36) of the patients with malignant MCA infarction undergoing DC. Furthermore, 59% (19 out of 34) patients developed epilepsy (33). Although a non-significant difference existed between TBI patients with or without seizures (incidence of 10.8%), the hospital stay prolonged significantly in the former group (35). Identifying the key risk factors predisposing to seizures and their effect on clinical outcomes needs more prospective studies.

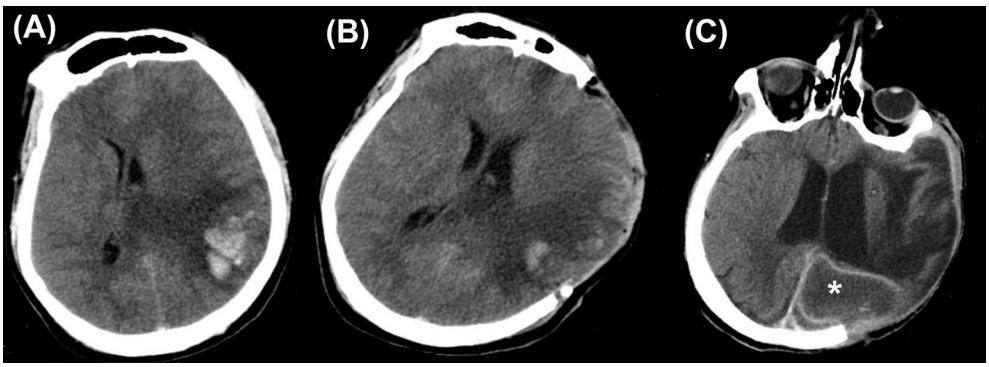

FIGURE 3 | Infections. Computed tomography depicting **(A)** a case of cerebral venous sinus thrombosis. **(B)** Post craniectomy showed a reduction in the midline shift. **(C)** However, this patient developed brain abscess (asterisk) 2 months later.

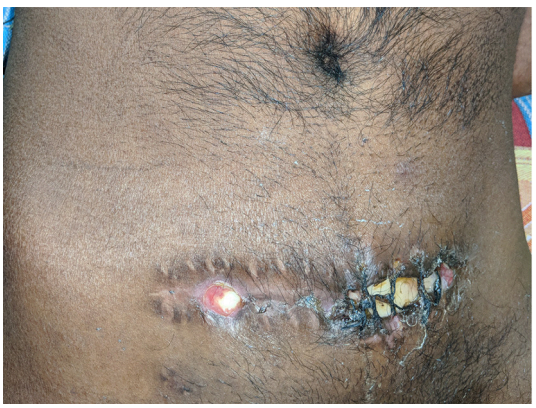

FIGURE 4 | Abdominal wound infection. A partially exposed bone flap is seen through the gaped abdominal storage site, predisposing to infections.

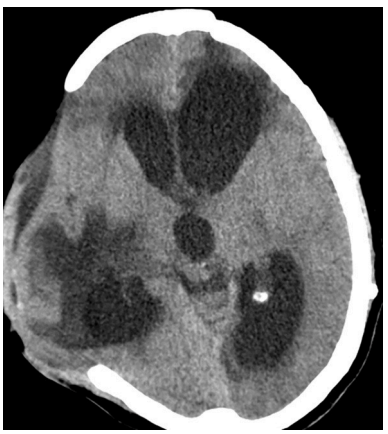

FIGURE 5 | Hydrocephalus. Computed tomography depicting a case of hydrocephalus after craniectomy.

In the case of TBI, Ban et al. reported that only about 3% developed seizures despite the use of anticonvulsants. Seizures disappeared in all the patients after increasing the dosage or after adding other antiepileptic drugs and that is a reasonable approach to follow in the first 2 weeks post injury (14). An early cranioplasty might serve to mitigate their occurrence, however, studies addressing this issue are currently lacking. Phenytoin and levetiracetam can be considered as antiepileptic drugs.

Late Complications

Subdural Hygroma

Subdural hygroma formation is another widely encountered complication after DC occurring in 27.4% (723/2,643) of patients with TBI and 12.5% (42/336) of patients with malignant infarction treated with DC in the total frequency calculation done by Kurland et al. (15). The putative mechanisms seems to be due to CSF flow abnormalities that develop after decompression possibly because of a disruption of the subarachnoid CSF pathways either due to trauma or surgical manipulation (38), or due to increased cerebral perfusion pressure (39). The common locations are the subdural, subgaleal, or interhemispheric areas (16, 40, 41), Though there is a speculative relationship with the development of hydrocephalus, subdural hygromas usually resolve spontaneously. But it has been shown to be associated with a worse neurological outcome (42). Effusions are thought to be reduced by a duraplasty.

Early pressure dressing applied 7–10 days after DC has been shown to reduce this complication in a small randomized controlled trial (43). A tense collection of fluid can rarely cause pressure on the brain due to a ball valve effect and has been termed external brain tamponade and such hygromas require drainage (16, 44, 45).

Hydrocephalus

Communicating hydrocephalus is another non-trivial complication of decompressive procedures because of the perturbation of CSF flow dynamics (**Figure 5**). Depending on the diagnostic criteria the incidence ranges from 0.7 to 86% (42). Bonis et al. showed by logistic regression analysis that the only factor that seemed to be associated with both subdural hygroma and hydrocephalus was if the superior margin of the craniectomy

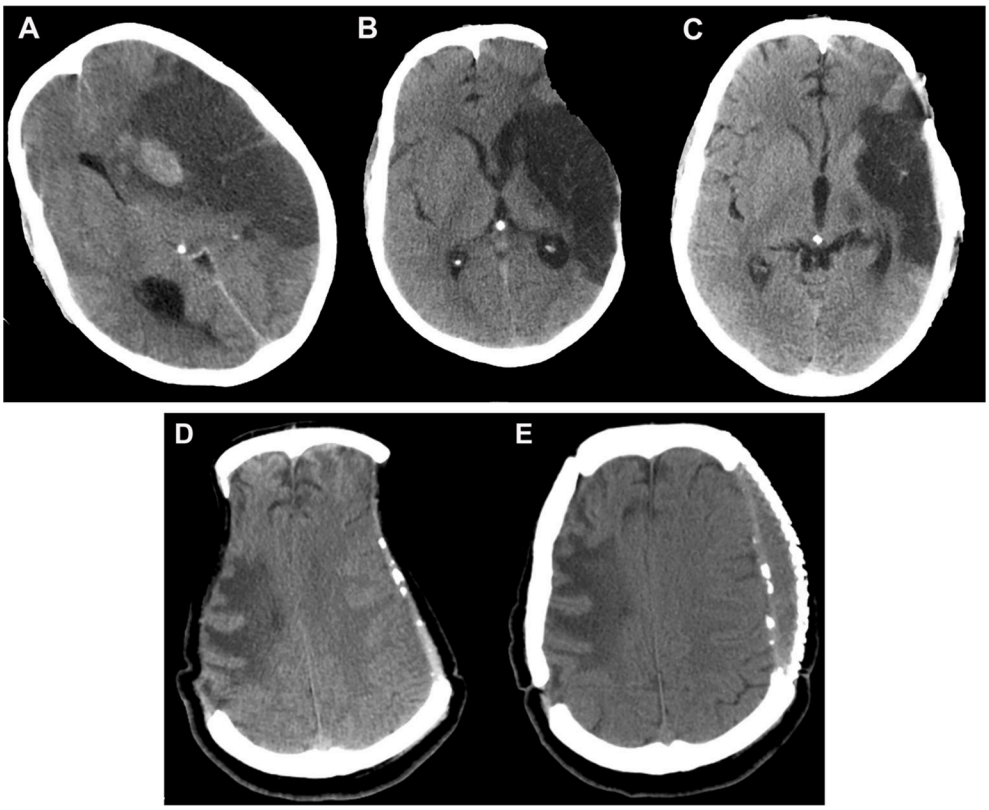

FIGURE 6 | Sunken flap syndrome. Computed tomography depicting **(A)** malignant hemispheric infarction, **(B)** sunken flap syndrome after 6 months, which improved **(C)** post cranioplasty. In a different patient **(D)**, bilateral sunken flap syndrome was observed 25 months post DC, and **(E)** improved after cranioplasty.
DC, decompressive craniectomy.

was closer than 2.5 cm to the midline (42). Development of hydrocephalus is also known to predict an unfavorable outcome (46). An early cranioplasty seems to mitigate the risk of post-traumatic hydrocephalus in a retrospective cohort study of 91,583 patients <21 years with TBI, in whom 846 developed post-traumatic hydrocephalus (47). Craniectomy without early cranioplasty was associated with markedly increased adjusted odds of post-traumatic hydrocephalus (aOR 3.67, 95% CI 2.66–5.07), an effect not seen in those undergoing cranioplasty within 30 days (aOR 1.19, 95% CI 0.75–1.89).

Syndrome of the Trephined

Syndrome of trephined has an overall prevalence of 10% (15). It was initially described by Grant and Norcross in 1939 (48). The sinking of the scalp due to lack of bony support (**Figure 6**) causes cerebral blood flow anomaly and dysfunction in the underlying cortex. Motor syndrome of the trephined is hypothesized to occur in patients who have had contusion induced low-density parenchymal areas. Delayed fluid shifts occur due to impaired CSF flow dynamics and this goes on to produce cerebral blood flow abnormalities and impaired motor function in a previously unaffected limb many months later (49). The syndrome can manifest in myriad ways and the most common symptoms identified in a recent systematic review were motor weakness (61.1%) followed by cognitive deficits (44.4%), language deficits (29.6%), altered level of consciousness (27.8%), headache (20.4%), psychosomatic disturbances (18.5%), seizures or electroencephalographic changes (11.1%), and cranial nerve deficits (5.6%) (50). It manifests either as new symptoms causing deterioration of the patient condition or as failure to retain the early gains. It could manifest as early as 3 days to as late as 7 years (with an average of 5 months). We must be mindful of the fact that only motor symptoms are obvious and it is quite easy to miss the diagnosis of syndrome of the trephined when non-motor symptoms like cognitive alterations occur. These symptoms, as well as, cerebral blood flow abnormalities improve dramatically after a cranioplasty. Yang has suggested it is safe to do early cranioplasty within 5–8 weeks to mitigate this risk (51) and a recent meta-analysis of observational studies involving 528 patients seems to support the possibility that neurological improvement is better in that group (52). If cranioplasty cannot be done due to a reason like infection and the patient is suffering from the effects of the sunken scalp flap, then a novel method of long standing scalp retraction using an external frame can be tried as described by Kim et al. (53).

Undue delay in cranioplasty and resorption of the bone flap after cranioplasty causes unsightly depression of the scalp. Temporal hollowing and chewing difficulty arises due

to extensive dissection of the temporalis muscle to get good decompression at the temporal base. A technique of en bloc detachment and anteroinferiorly turning of the temporal muscle using a clover leaf scalp incision has been described by Missori et al., in 21 patients undergoing DC. They reported good aesthetic results and all eligible patients reported normal chewing ability (54).

SUMMARY

Decompressive craniectomy for intractable intracranial hypertension due to stroke or traumatic brain injury is a proven treatment for reducing mortality and there is some evidence, albeit controversial (55), that it improves the fraction of good grade survivors. But the therapy is fraught with multiple, non-trivial complications that need to be anticipated and treated early (see **Table 1** for an overview). Doing a sufficiently large cranioplasty to avoid cerebral herniation and having a low threshold diagnosing for progression of bleeds in the immediate postoperative period cannot be over emphasized. An early cranioplasty, preferably within 12 weeks, as soon as the brain is lax, is advisable to prevent long-term complications of DC.

AUTHOR CONTRIBUTIONS

MG, NS prepared, edited, structured, revised, and critically reviewed the manuscript. DS, SK, and DB critically reviewed and accepted the final draft. BD edited, critically reviewed, and accepted the final draft.

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REVIEW
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Role of Decompressive Craniectomy in Ischemic Stroke

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Ischemic stroke is one of the leading causes for death and disability worldwide. In patients with large space-occupying infarction, the subsequent edema complicated by transtentorial herniation poses a lethal threat. Especially in patients with malignant middle cerebral artery infarction, brain swelling secondary to the vessel occlusion is associated with high mortality. By decompressive craniectomy, a significant proportion of the skull is surgically removed, allowing the ischemic tissue to shift through the surgical defect rather than to the unaffected regions of the brain, thus avoiding secondary damage due to increased intracranial pressure. Several studies have shown that decompressive craniectomy reduces the mortality rate in patients with malignant cerebral artery infarction. However, this is done for the cost of a higher proportion of patients who survive with severe disability. In this review, we will describe the clinical and radiological features of malignant middle cerebral artery infarction and the role of decompressive craniectomy and additional therapies in this condition. We will also discuss large cerebellar stroke and the possibilities of suboccipital craniectomy.

Keywords: stroke, craniectomy, middle cerebral artery infarction, posterior circulation stroke, prognosis

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INTRODUCTION

The increasing burden of stroke is one of the main challenges for health providers worldwide. Stroke is ranked as the second most common cause of death globally and the most common cause of acquired disability in adults (1, 2). Considerable efforts have been made to enhance the quality of care and medical management in ischemic stroke patients. Intravenous thrombolysis with rt-PA administered within 4.5 h from symptom onset can significantly improve patients' outcome (3). Furthermore, evidence from recent randomized controlled trials underlines the efficacy of endovascular treatment with mechanical removal of occluding blood clots via catheterization (3). However, only a minority of patients (up to 25% in well-organized stroke centers) receive intravenous thrombolysis, and its benefit in large vessel occlusion is limited by an overall low recanalization rate of approximately 20% (4). And although endovascular thrombectomy (EVT) has been shown to be effective in large vessel occlusive stroke within 24 h from stroke onset, it is hampered by the availability of EVT-capable centers (5–9). Furthermore, the patients may suffer from significant ischemic brain damage despite timely recanalization, a situation coined by the term "futile recanalization (10)."

Patients with large hemispheric infarction may suffer from increasing intracranial pressure (ICP) resulting in cerebral herniation and subsequent mechanical and ischemic damage of healthy cerebral territories (11). With decompressive craniectomy (DC), a proportion of the skull is surgically removed to allow the edematous brain tissue to herniate to the outside and thus

preventing neuronal damage in other regions of the brain (12) (**Figure 1**). Two principal groups of stroke patients who may benefit from craniectomy can be distinguished: First, patients with large cerebellar infarction and subsequent suboccipital craniectomy (SOC); and secondly patients with large infarction of the middle cerebral artery territory, also called malignant middle cerebral artery infarction (MMCAI). The latter will be the main topic of this review, therefore we will only briefly comment on surgical options in patients with space-occupying cerebellar infarction.

MALIGNANT MIDDLE CEREBRAL ARTERY INFARCTION

In 1–10% of all patients with acute middle cerebral artery occlusion, the subsequent ischemic stroke can be classified as "malignant," defined by ischemic brain tissue large enough to cause considerable increase of ICP and potential cerebral herniation (13). Clinically, the patients present with severe hemispheric symptoms including hemiparesis or hemiplegia, loss of visual field, gaze deviation and, depending on the affected hemisphere, neglect or aphasia. Patients may also show an impaired level of consciousness, nausea, vomiting, papillary changes and papilledema as signs of increased ICP (13). The severity of neurological deficits is usually measured with the National Institute of Health Stroke Scale (NIHSS) score, with higher scores indicating more severe deficits (range 0–42). Patients with MMCAI will typically have scores >15 points if the non-dominant hemisphere is affected and >20 points if the dominant hemisphere is affected (14). The long-term functional outcome of patients with stroke is typically measured with the modified Rankin Scale (mRS) score, with 0 indicating no symptoms and 6 indicating death (**Table 1**).

Not all patients with middle cerebral artery occlusion develop MMCAI and several studies have attempted to establish predictors of possible mass effect with subsequent clinical deterioration. In a prospectively collected dataset, 19% of patients with ischemic stroke due to middle cerebral artery occlusion had MMCAI with higher NIHSS scores being an independent predictor (15). Furthermore, history of arterial hypertension, increased blood pressure following the first 12 h after stroke onset, female sex, and congestive heart failure have been identified as independent predictors in earlier studies (14, 16). Younger age was also associated with MMCAI, possibly due to lack of age-dependent brain atrophy leading to earlier mass effect of ischemic territories, and fewer intracerebral vessel collaterals due to lower rates of atherosclerotic stenosis in this population (14, 17).

Several neuroradiological predictors for MMCAI have been identified. CT of the brain is still the most widely used imaging method in the assessment of acute stroke (18). Whilst ischemic changes appear as hypodense areas in the affected territories, proximal occlusion of the middle cerebral artery can be detected with CT angiography (19). In cases of middle cerebral artery occlusion, ischemic changes on plain CT in more than 50% of the corresponding territory are independently associated with fatal brain swelling (14, 16).Measurement of optic nerve sheath diameter, eyeball transverse diameter and the ratio of both on plain CT may identify patients with high risk of developing a MMCAI (20). A similar approach has been made with duplexsonography of the optic nerve (21). CT Perfusion may also

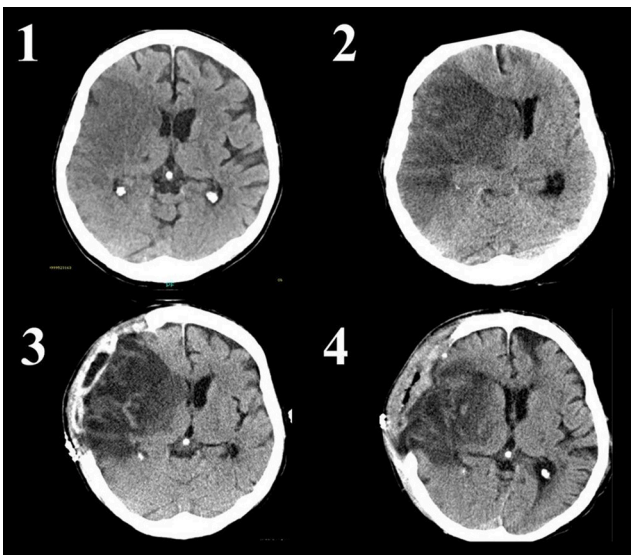

FIGURE 1 | Native CT scans of a patient with infarction of the complete right middle cerebral artery territory. A systemic or endovascular therapy was not conducted due to late arrival and already visible ischemic changes. Image 1 shows the ischemic tissue as darker (hypodense) area without significant mass effect. Image 2 reveals progressive edema of the ischemic tissue with visible midline shift. The occipital horn of the left lateral ventricle is enlarged due to disturbance of cerebrospinal fluid circulation. The patient was alert but deteriorated with reduced level of consciousness immediately prior the CT. Image 3 shows a CT-scan 1 day after decompressive craniectomy. The midline shift and enlargement of the left occipital horn are decreasing, whereas brain tissue is herniating through the skull defect. Image 4 is a CT scan 8 days after decompressive surgery. Midline shift has nearly normalized. The now visible defect on the left frontal part of the brain is caused by an old injury of the patient.

TABLE 1 | Modified Rankin Scale (mRS).

Score	Description
0	No symptoms
1	No significant disability. Able to carry out all usual activities, despite some symptoms
2	Slight disability. Able to look after own affairs without assistance, but unable to carry out all previous activities.
3	Moderate disability. Requires some help, but able to walk unassisted.
4	Moderately severe disability. Unable to attend to own bodily needs without assistance, and unable to walk unassisted.
5	Severe disability. Requires constant nursing care and attention, bedridden, incontinent.
6	Dead

be useful in the detection of malignant edema in ischemic stroke patients (22–24). Furthermore, clot burden, proximity of clot in the vessel, permeability, and poor intracranial collaterals have been described as CT based predictors for malignant cerebral edema (25).

Imaging assessment of stroke by MRI has the advantage of higher sensitivity for early ischemic changes than CT; however, the examination is more time consuming and suffers from lower availability (18). In cases of middle cerebral artery stroke, one study found a high risk of herniation in patients with an infarct volume >145 cc on diffusion-weighted-images (DWI), whilst another analysis found a high specificity of 98% for the development of MMCAI if the DWI lesion was >82 cc (15, 26).

Prognosis of patients with MMCAI is poor with a mortality rate of approximately 80% if treated conservatively (13, 27). There is only insufficient evidence that additional non-surgical therapeutic regimes other than specialized care on a stroke unit or intensive care unit can improve patients' outcomes. Hence DC should be considered in patients with MMCAI.

DECOMPRESSIVE CRANIECTOMY IN MALIGNANT MIDDLE CEREBRAL ARTERY STROKE

Current Evidence–Randomized Controlled Trials

The procedure of DC to reduce ICP due to cerebral edema is more than 100 years old and numerous studies have addressed this issue so far (28). In the following we will focus on randomized controlled trials (RCTs, **Table 2**) and meta-analyses. These studies differ in their design, inclusion criteria and primary and secondary endpoints. All studies have in common that patients were randomized either to surgery in form of DC or to best medical care.

- In the multicenter ***DE*compressive *C*raniectomy *I*n *MAL*ignant MCA Infarction (DECIMAL)** trial from France, patients aged 18–55 years with MMCAI were included and either assigned to DC with best medical care or best medical care only (29). MMCAI was defined by three criteria: NIHSS score >15 points (including at least one of three points in the section "reduced consciousness"), involvement of more than 50% of the middle cerebral artery vascular territory on plain CT, and infarct volume of more than 145 cc on MRI- DWI. In almost 4 years, 38 patients were included with 20 patients randomized to DC and 18 to best medical care only. Primary outcome parameter was "favorable functional outcome" 6 month after the index event, defined as mRS scores of 0–3. The safety monitoring committee recommended stopping the study due to slow recruitment, significant difference of mortality in the two groups, and to organize a pooled analysis with the other European RCTs (see below). Looking at the primary outcome parameter, 25% of the patients in the DC group had a favorable functional outcome compared with 5.6% of patients in the best medical treatment group ($p = 0.18$). After 1 year, these numbers increased to 50 vs. 22.2%, respectively ($p = 0.10$). Regarding mortality, DC lead to a 52.8% absolute reduction of death, whereas only 4 out of the 18 patients (22.2%) in the non-surgery group survived.

- In the ***De*compressive *S*urgery for the *T*reatment of Malignant *In*farction of the Middle Cerebral Arter*y* (DESTINY)** trial conducted in Germany, patients aged 18–60 years were randomized either to surgery or conservative therapy (30). Due to the expected overwhelming advantage of DC regarding mortality, this study used a sequential design for outcome parameters: first endpoint was mortality at 30 days. After this endpoint was reached, enrollment was interrupted and the sample size was recalculated based on good functional outcome, defined as mRS scores of 0–3 vs. 4–6, at 6 months. Clinical inclusion criteria were a NIHSS score of >18 if the non-dominant hemisphere was affected and >20 if the dominant hemisphere was affected. Furthermore, patients had to have a decreased level of consciousness of ≥1 on the item 1a of the NIHSS score. Imaging criteria were affection of >2/3 of the middle cerebral artery territory including at least a part of the basal ganglia. Patients could be included if the ipsilateral anterior or posterior cerebral artery territory were also infarcted. After the inclusion of 32 patients, a significant reduction in mortality was evident with survival of 15 of 17 (88%) patients in the DC group compared with 7 of 15 (47%) patients in the conservative group. After 6 and 12 months, there was no statistically significant difference in the rate of favorable functional outcome in both patient groups (47 vs. 27%, respectively; $p = 0.23$). The projected sample size was calculated as 188 patients, but the steering committee recommended the termination of the study in favor of a pooled analysis of the three European RCTs (see below).

- The Dutch ***H*emicraniectomy *A*fter *M*iddle Cerebral Artery Infarction With *L*ife-Threatening *E*dema *T*rial (HAMLET)** included patients 18–60 years old (31). Patients could be randomized up to 96 h from symptom onset, imaging criteria for inclusion was affection of two-third or more of the middle cerebral artery territory with formation of space-occupying edema. Regarding clinical status prior randomization, patients had to have a NIHSS score of ≥16 for right-sided ischemia and of ≥21 for left sided ischemia as well as a decreased level of consciousness defined by a Glascow Coma Scale ≤13 for right-sided lesions or an eye and motor score of ≤9 for left-sided lesions. The primary endpoint was defined as "good outcome" (mRS scores 0–3 vs. 4–6) at 12 months. Secondary outcome measures included mRS score at 3 years (32). Of 64 patients included, 50% were either randomized to DC or best medical care. After 1 year, DC had no effect on good functional outcome (25 vs. 25%, respectively; absolute risk reduction [ARR] 0%, 95%CI −21–21; $p = 1.00$), whilst significantly reducing case fatality (ARR 38%; 95%CI 15–60; $p = 0.002$). In the three-year analysis, DC also had no effect on good functional outcome (26 vs. 25%, ARR 1%, 95%CI −21–22; $p = 0.94$). The study was stopped prematurely for futility as it was considered highly unlikely that a significant difference of the primary outcome parameter between the two groups could be detected.

- A **Chinese study**, conducted at four study sites, included patients aged 18–80 years (33). This study was stopped after 47 patients were enrolled due to a significant difference in poor outcome (defined as mRS score 5–6) favoring DC. After 6

TABLE 2 | Overview of the randomized controlled trials (RCTs).

Study name	Age (years)	Inclusion from symptom onset (hours)	Imaging criteria	Clinical criteria	Primary outcome parameter	Main finding	Patients included, n (DC/BMT)
DECIMAL	18–55	<24	>50% ischemic MCA territory; MRI-DWI infarct volume >145 cc	NIHSS >15; NIHSS 1a ≥1	mRS 0–3 at 6 months	52.5% absolute mortality reduction with DC compared to BMT ($p < 0.0001$); no significant difference between DC and BMT regarding mRS 0–3	38 (20/18)
DESTINY I	18–60	>12 to <36	≥2/3 MCA territory with basal ganglia; with/without ACA/PCA territory	NIHSS >18 (non-dominant) or >20 (dominant); NIHSS 1a ≥1	Sequential design: mortality after 30 days; mRS 0–3 vs. 4–6 at 6 months	Mortality reduction from 88% to 47% with DC after 30 days ($p = 0.02$)	32 (17/15)
HAMLET	18–60	<96	≥2/3 MCA territory; formation of space occupying edema	NIHSS ≥16 (right) or ≥21 (left); NIHSS 1a ≥1; GCS <13 (right-sided) or GCS (eye and motor score) < 9 (left-sided)	mRS 0–3 vs. 4–6 at 12 months	DC with no effect on primary outcome measure but significant reduction of case fatality (ARR 38%)	64 (32/32)
Zhao et al.	18–80	<48	≥2/3 MCA territory; with/without ACA/PCA territory; space-occupying edema	GCS (eye and motor score) ≤9	mRS 0–4 vs. 5–6 at 6 months	Reduction of mortality (DC 12.5% vs. BMT 60.9 %, $p = 0.001$) and mRS 5–6 (DC 33.3% vs. BMT 82.6 %, $p = 0.001$)	47 (24/23)
HeADDFIRST	18–75	<96	≥50% ischemic MCA territory(<5h) or complete MCA infarction (<48h)	NIHSS ≥18; NIHSS 1a <2	survival 21 days	Non-significant reduction of mortality at 21 days (DC 21% vs. BMT 40%, $p = 0.39$)	24 (14/10)
DESTINY II	>60	<48	≥2/3 MCA territory with basal ganglia	NIHSS >14 (non-dominant) or >19 (dominant), reduced level of consouscness on NIHSS	mRS 0–4 at 6 months	Significant reduction of severe disability (mRS scores 5–6: DC 38% vs. BMT 18%, $p = 0.04$)	112 (49/63)
Slezins et al.	>18	<48	≥2/3 MCA; with/without ACA/PCA territory or cerebral infarct volume >145 cc	NIHSS >15	mRS 0–4 vs. 5–6 at 12 months	Significant mortality reduction (DC 45.5% vs. BMT 7.7%, $p = 0.03$)	24 (11/13)
HeMMI	18–65	≤72	≥2/3 MCA territory; with/without ACA/PCA territory	GCS 6–14 (right-side) or 5–9 (left-side); GCS 15 and NIHSS ≥1a	mRS 0–3 vs. 4–6 at 6 months	No significant differences (DC 23.1% vs. BMT 38.4%, $p = 0.476$)	29 (16/13)

ACA, indicates anterior cerebral artery; ARR, absolute risk reduction; BMT, best medical treatment; DC, decompressive craniectomy; GCS, Glasgow Coma Scale; MCA, middle cerebral artery; mRS, modified Rankin Scale; NIHSS, National Institute of Health Stroke Scale; PCA, posterior cerebral artery.

months, 8 of 24 (33.3%) patients who received DC compared to 19 of 23 patients (82.6%) in the conservative arm had a mRS score >4 [adjusted risk ratio [aRR] 49.3%, 95%CI 24.9–73.7; $p = 0.001$], and 14 of 23 (60.9%) patients who received best medical care vs. 3 of 24 (12.5%) patients who received DC had died (aRR 48.4%, 95%CI 24.4–72.3; $p = 0.001$). There was no significant difference between both groups regarding poor functional outcome (mRS scores >3) at 6 months and 12 months ($p = 0.209$ and $p = 0.272$, respectively).

- The ***He*micraniectomy *a*nd *D*urotomy Upon *D*eterioration *F*rom *I*nfarction-*R*elated *S*welling *T*rial (HeADDFIRST)** was a randomized pilot study to gain information for the design of a phase III trial (34). Based in the United States, a two-step approach for the inclusion of patients was selected: first, all patients aged 18–75 years with unilateral middle cerebral artery infarction who were responsive to minor stimulation and had a NIHSS score ≥ 18 points were screened. If these patients fulfilled the imaging criteria (more than 50% of the middle cerebral artery territory affected on CT performed <5 h from symptom onset or complete infarction on CT performed <48 h from symptom onset), patients were eligible for enrollment and treated according to standardized medical management, closely monitored for clinical deterioration. Patients were eligible for randomization to best medical care vs. DC if at least one of the following criteria were met: midline-shift of the horizontal anterior septum pellucidum of ≥7.5 mm with unchanged or worsened neurological status, or midline-shift of the horizontal pineal ≥4 mm with depression of arousability to the level of effortful awakening. After the screening of 4,909 patients, only 26 patients were randomized of whom 10 patients received best medical treatment and 14 patients received additional DC (one patient was not treated according to protocol due to the decision of the treating physician and from another patient the spouse withdrew consent). After 21 days, 4 of 10 (40%) patients in the conservative arm compared with 3 of 14 (21%) patients who received DC had died (primary study endpoint, $p = 0.39$). At 6 months, the mortality remained 40% (4 of 10 patients) in the best medical treatment group compared with 36% (5/14) in the DC arm.

- After the effect of DC on improved functional outcome had been demonstrated in the pooled analyses of the European randomized controlled trials in patients aged <60 years (see below), the **DESTINY II** trial sought to analyze the effect of DC in patients >60 years old (35). The primary endpoint was a mRS score from 0 to 4 at 6 months. Besides age, patients had to have a NIHSS score >14 (or 19, if the non-dominant hemisphere was affected), a reduced level of consciousness and imaging evidence of infarction in at least two thirds of the middle cerebral artery territory. In 13 German centers a total of 112 patients were enrolled. The data and safety monitoring board recommended to stop enrollment after 82 patients had been assessed clinically at 6 months. Median age was 70 years in both groups. Regarding the primary end point in the intention-to-treat population, 20 of 49 patients (41%) in the DC group vs.10 of 63 patients (16%) in the conservative group had a mRS score of 0–4 (bias corrected 38 vs. 18%, [Odds ratio]OR 2.91, 95%CI 1.06 to 7.49; $p = 0.04$). Mortality at 12-months was 43% (20/47) of the patients who received DC vs. 76% (47/62) in the conservative arm. No patient, neither in the control group nor the DC group, had a mRS score of 0–2 (i.e., functional independence), and only 7% of the patients who underwent DC and 3% of patients in the conservative group had a mRS score of 3 at 12 months (i.e., able to walk without assistance).

Further monocentric studies have assessed the effect of hemicraniectomy on functional outcome in randomized trials.

- One **monocentric study from Latvia** enrolled 28 patients, inclusion criteria were age 18 years, MMCAI defined by CT or MRI with at least 50% infarction in the middle cerebral artery territory (or 145 cc infarct volume), NIHSS score >15 points and possibility to perform surgery within 48 h after symptom onset (36). Primary endpoint was mRS score 0 to 4 vs. 5–6 at 1 year. After exclusion of 3 patients due to time frame violation (surgery >48 h) and one patient due to absence of increased ICP after implantation of a monitoring gauge, 24 patients were finally analyzed of whom eleven (45.8%) received DC and 13 (54.2%) patients best medical treatment. After 1 year, 5 of 11 patients (45.5%) with DC survived compared to 1 of 13 patients (7.7%) in the best medical treatment group (p=0.03). Among the survivors, 3 of 5 patients in the DC group had a mRS score of 3 and two patients had a mRS score of 2, whereas the surviving patient with best medical management had a mRS score of 4.

- The second monocentric study (***He*micraniectomy for *M*alignant *M*iddle cerebral *I*nfarction, HeMMI**) was conducted in the Philippines and included patients aged 18–65 with middle cerebral artery infarction, a Glagow Coma Scale (GCS) score of 6–14 for patients with right sided infarction or 5–9 for patients with left sided infarction, or a GCS score of 15 but clinical deterioration of ≥1 point in the consciousness item of the NIHSS score, and infarction of more than 50% of the middle cerebral artery vascular territory on plain CT (37). Primary outcome parameter was mRS score 0–3 vs. 4–6. Secondary outcome parameters were mRS scores 0–4 vs. 5–6 and mortality. Of 29 patients enrolled, 16 (55.2%) received DC and 13 (44.8%) received best medical care. The study is in so far unique, as three patients in the conservative arm eventually received DC due to secondary deterioration and one patient in the DC group did not receive surgery due to acute myocardial infarction. Three patients in the DC arm and two patients in the conservative arm were lost to follow-up. Finally 24 patients (13 [54.2%] with DC vs. 11 [45.3%] with best medical care) were analyzed. At 6 months, there was no statistically significant difference between the two groups regarding all primary and secondary outcome parameters.

- Another monocentric trial, ***DE*compressive surgery for the treatment of *M*alignant *I*nfarction of the middle cerebral artery: a randomized, controlled trial in a *TUR*kish population (DEMITUR)** was conducted in Turkey. To the best of our knowledge, this study has not yet been published.

Current Evidence–Meta-Analyses

As mentioned above, the first meta-analysis was conducted with pooled data of the first three European RCTs (HAMLET, DECIMAL and DESTINY) (38). The design of this analysis was developed when the studies themselves were still recruiting patients and the outcome measures were defined without

knowledge of the results of the individual studies. Patients aged 18–60 were included and primary endpoint was a dichotomized mRS score at 1 year (0–4 vs. 5–6). Secondary endpoints were case fatality at 1 year and a dichotomized mRS score of 0–3 vs. 4–6. Only patients with surgery performed within 48 h after symptom onset were included. In summary, the data of 93 patients were analyzed with 51 patients (55%) randomized to DC and 42 patients (45%) to conservative treatment. Regarding the primary outcome measure, significantly more patients in the best medical treatment group had a mRS score of 5–6 (32/42 [76.2%] vs. 13/51 [25.5%], OR 0.10, 95%CI 33.9–68.5; $p < 0.0001$). The difference between the two groups remained significant on the outcome parameter mRS score 4–6 (conservative arm 33/42 [78.6%] vs. DC arm 29/51 [56.9%]; OR 0.33, 95%CI 4.6–40.9), $p = 0.014$) and death (30/42 [71.4%] vs. 11/51 [21.6%]; OR 0.10, 95%CI 33.3–67.4, $p = 0.0001$) at 12 months.

- A Cochrane review of the three European trials included 134 patients aged 60 or younger (69 patients [51.5%] randomized to DC and 65 patients [48.5%] randomized to best medical treatment) (39). DC significantly reduced the risk of death (OR 0.19, 95%CI 0.09–0.37) and very poor functional outcome (mRS scores 5 or 6; OR 0.26, 95%CI 0.13–0.51) at the end of follow-up period, whilst there was no significant difference regarding mRS scores 4 to 6 (OR 0.56; 95%CI 0.27 to 1.15).

- One meta-analysis published in 2015 included the four European trials (HAMLET, DECIMAL, DESTINY I and II) as well as HeADDFIRST and the Chinese multicentric study, comprising a total of 317 patients (156 [49.2%] in the surgery arm and 161 [50.8%] in the conservative arm) (40). Individual patients were analyzed and a pooled odds ratio was calculated. Here a significant reduction of mortality 6 months after the index event emerged (OR 0.19, 95%CI 0.10–0.37). This difference remained significant at 12 months (OR 0.17, 95%CI, 0.10–0.29). Patients with DC more often achieved a mRS score of 4 at six (OR 3.29, 95%CI 1.76–6.13) and 12 months (OR 4.43, 95%CI 2.27 to 8.66). A similar Meta-Analysis including the same trials came to comparable results (41).

- The most recent Meta-Analysis was published in 2016 and included DECIMAL, HAMLET, DESTINY I, and II, HeADDFIRST, the Chinese multicentric study and the monocentric study from Latvia (42). In summary, 338 patients were included in this analysis with 165 (48.8%) allocated to DC and 173 (51.2%) to best medical care. Regarding death, the authors found that the patients who received DC had a significantly lower mortality (RR 2.05, 95%CI 1.54–2.72; $p < 0.00001$). Surgery increased the likelihood to survive with a mRS 0 to 3 (RR 1.58, 95%CI 1.02–2.46; $p = 0.04$) or mRS 0 to 4 (RR 2.25, 95% CI 1.51–3.35, $p < 0.0001$).

In summary, these studies show a striking advantage of the surgical therapy concerning mortality. This seems to be achieved at the expense of a greater share of patients surviving with a mRS score of 4 and higher. It should be noted that most stroke studies have defined favorable functional outcome as mRS scores 0 to 3, 0 to 2 or even 0 to 1 (in a general stroke population), whereas some MMCAI trials and above mentioned meta-analyses adopted a definition of mRS scores 0–4 for favorable functional outcome instead. This may be justified by the fact that – due to the severity of the disease - it is unlikely that a decent amount of patients with MMCAI could survive with the ability to walk without assistance. However, the definition of "favorable outcome" in these patients remains conflicting (43). Although DC and its technique may be comparable in all studies, best medical treatment was only defined in some of the trials, and we can assume that patients in both treatment groups were treated differently and not all of these differences were reported. The DESTINY II trial showed that DC is also effective in patients aged older 60 years, therefore a strict age threshold for the selection of patients who may qualify for surgical therapy cannot be recommended (35). It should be noted that the percentage of patients with severe disability was significantly higher (19 vs. 4%) and the percentage of patients with moderate disability significantly lower (6 vs. 43%) when compared with patients ≤60 years.

Timing for DC

Although all RCTs defined a time window of inclusion, none of the aforementioned trials addressed the issue of the ideal timing for DC. The DECIMAL trial demanded randomization not later than 24 h after symptom onset with start of surgical procedure no later than 6 h after randomization (29). In DESTINY I, patients could be randomized if a surgical procedure could be performed between 12 and 36 h after symptom onset, with surgery performed not later than 6 h after randomization (30). In contrast, the HAMLET trial allowed patients to be randomized up to 96 h after symptom onset, with start of treatment up to 3 h after randomization (31). Here, median time from onset of symptoms to randomization was 41 h in the surgical arm and 45 h in the best medical treatment arm. About one third (34%) of all patients in the surgical arm were randomized later than 48 h after the index event, compared to 44% in the conservative arm. As HAMLET was negative regarding its primary endpoint, there is currently no evidence that DC improves functional outcome when it is delayed for >48 h and up to 96 h after stroke onset. Moreover, in the Latvian monocentric trial, three patients underwent surgery later than 100 h after symptom onset, however, none of these patients survived (36). The European meta-analysis included only patients with surgery performed no later than 48 h after symptom onset, and DESTINY II followed this pattern (29, 35).

Physicians commonly face the dilemma either to wait until patients with large hemispheric stroke deteriorate clinically, thus accepting a risk of secondary tissue damage due to increased ICP before DC is initiated—or to perform DC preemptive before clinical deterioration, accepting to treat patients aggressively who potentially may not require DC and therefore do not benefit from this procedure. Cerebral edema due to ischemic stroke is expected to culminate on day 2–5 after the index event (11, 44). However, although almost 70% of patients with stroke deteriorate due to cerebral edema within 48 h after symptom onset, roughly one third of patients experience worsening after this time frame (45). There are only few publications that address the timing of DC. In a national inpatient sample analysis from the United States, from a total of 1,301 patients with DC after stroke, 287 patients (22.1%) underwent surgery within 24 h, 726 (55.8%) within 48 h, and 999 (76.8%) within 72 h (46). The impact of timing was analyzed continuously and dichotomized

according to the aforementioned time windows. Regarding in-hospital mortality, neither the continuously (OR 1.06, 95%CI 0.97–1.15; $p = 0.21$) nor the dichotomously conducted analyses showed a significant difference (OR 1.03, 95%CI 0.74–1.42; $p = 0.87$; OR 1.00, 95%CI 0.76–1.33; $p = 0.98$ and OR 1.11, 95%CI 0.80–1.55; $p = 0.53$, respectively). However, in the continuous analysis, later DC was associated with greater odds of discharge to institutional care (OR 1.17, 95%CI 1.05–1.31; $p = 0.005$) and of sustained poor outcome, defined by the - in this context seldom used - Nationwide Inpatient Sample Subarachnoid hemorrhage Outcome Measure (NIS-SOM) (OR 1.12, 95%CI 1.02–1.23; $p = 0.02$). Using a dichotomized approach, whilst surgery within 24 h compared to 48 h was not associated with different outcomes, DC performed within 72 h increased the odds for discharge to institutional care or poor outcome (OR 1.59, 95%CI 1.08–2.34; $p = 0.02$ and OR 1.52, 95%CI 1.07–2.16; $p = 0.02$, respectively). Although this study supported to perform DC within 72 rather than 48 h, a subgroup analysis showed a strong association of herniation with mortality (OR 1.70, 95%CI 1.14–2.56; $p = 0.009$), discharge to institutional care (OR 1.36, 95%CI 1.06–1.75; $p = 0.02$) and sustained poor outcome (OR 1.31, 95%CI 1.01–1.71; $p = 0.045$), indicating the importance to perform DC before the development of critically increased ICP rather than fixed time windows.

A recent monocentric randomized trial divided patients with MMCAI into two groups with DC performed after clear neurological deterioration vs. ultra-early DC within 6 h after presentation (47). Of 46 consecutively admitted patients, 27 patients (59%) were allocated to surgery after clinical or radiological deterioration and 19 patients (41%) to ultra-early surgery. There was a significant reduction of mortality favoring the ultra-early DC group [14 patients (52%) vs. 2 patients (10.5%), $p < 0.05$]. Furthermore, the authors report a statistically significant improvement of functional outcome in the ultra-early DC group. The study shows unique features especially concerning the best medical treatment with maintenance application of mannitol, administration of intravenous phenytoin and use of corticosteroids. Furthermore, imaging and clinical criteria for inclusion in this study are not described in detail. Therefore, the generalizability of this study must be questioned.

As there is currently no evidence that DC improves functional outcomes when it is delayed for >48 h and up to 96 h after stroke onset, patients with MMCAI who are eligible for DC should receive surgery within 48 h from symptom onset (31, 38, 48).

Special Care and Additional Therapy in Patients With MMCAI and DC

Evidence supporting sole conservative treatment to control brain edema in patients with stroke is lacking (49). However, it can be assumed that at least some patients receive antiedema therapy in addition to DC, and all trial protocols allowed for corresponding adjuvant therapies according to national guidelines in these patients (29–31, 35). However, treatment protocols differed remarkably between the studies regarding extent and timing of treatment initiation and in most cases were left at the discretion of the treating physicians. Moreover, data on the duration of analgosedation following hemicraniectomy is lacking.

Besides common critical care with airway management, positioning of the patient, optimization of blood pressure and volume status, the following three procedures are commonly discussed as treatment options for patients with MMCAI.

Measurement of Intracranial Pressure (ICP)

Critically increased ICP can be clinically detected by reduced level of consciousness, brain stem symptoms resulting from transtentorial herniation and an overall worsening of the neurological status. Treatment for intracranial mass effect should ideally be initiated before the onset of clinical symptoms, thus preventing further damage of brain tissue (50). Repeated imaging via CT or MRI can reveal signs of increased ICP like midline shift, damage to primarily unaffected territories of the brain or enlargement of the intracranial cavities as a sign of cerebrospinal fluid circulation disturbance (51). However, it is not a real-time (i.e., bed-side) method and it is therefore challenging to determine the frequency in which these neuroradiological tests should be performed—particularly in patients with unchanged clinical status. Furthermore, whilst MRI can be difficult to perform in these often unstable patients, CT is associated with a notable radiation exposure. Hence the implantation of an ICP probe should be considered in patients with DC after MMCAI.

There is still controversy regarding the usefulness of these probes in patients with ischemic stroke. Whilst some earlier studied had promising results indicating a direct association between ICP values and clinical outcome and neuroradiological findings, other studies have revealed that patients could develop serious mass effect and even papillary disturbances while normal ICP values are collected (52, 53). Furthermore, although ICP values between 7 and 15 mmHg are considered normal and it is usually recommended to treat values above 20–22 mmHg, ICP values should always be seen in context with the cerebral perfusion pressure (CPP), the difference of middle artery pressure (MAP) and ICP (CCP=MAP-ICP) (54–56). Here a CPP value >50–60 mmHg should be achieved (55).

In summary, the ICP measurement can be helpful in the treatment of patients with DC after ischemic stroke; however, the interpretation values should be done in the context with clinical and neuroradiological findings. This is even more important as the ICP does not increase linearly but steeply above thresholds >25 mmHg. Therefore the decision to perform DC should not be based solely on ICP values but on clinical signs and current guidelines.

Osmotherapy

One of the most common non-surgical ways to reduce elevated ICP is osmotherapy which is overall applied by almost 90% of neurocritical care physicians (57). The basic principle of osmotherapy consists of the administration of certain substances which elevate the blood osmolality but are unable to pass the blood-brain barrier (48, 58). Following the osmotic gradient, fluid is extracted from the brain tissue into the blood stream, therefore reducing intracranial mass effect.

Although the physiological and pathophysiological principles of osmotherapy are reasonable, data regarding its effect on ICP and functional outcome are ambiguous: whilst some studies have found that osmotherapy can effectively reduce ICP, others have failed to do so, and the overall effect on patients' outcomes remains uncertain. A recent prospective cohort study with 922 included patients revealed a higher rate of dependency (97.7 vs. 58.5%; $p < 0.001$) and mortality (46.5 vs. 5.6%; $p < 0.001$) in patients who received mannitol (59). However, <10% of the patients in the study population received mannitol and the authors do not comment if any or how many patients received DC.

The general concept of osmotherapy is not without criticism. One may argue that an intact blood-brain barrier, which is critical to establish an osmotic gradient, is absent in injured brain tissue, therefore the administration of osmotic agents may be without beneficial but even detrimental effects (60).

In summary, the pure effect of osmotherapy and its effect on functional outcome is a matter of debate. Randomized controlled trials regarding the effect of osmotherapy on clinical outcomes are lacking, although several guidelines recommend its usage in ischemic stroke patients (48, 60). With mannitol, glycerol and hypertonic saline solution being the most commonly used substances, there is no clear evidence of benefit of any of these osmotherapeutic regimes (48, 49, 55, 60). Osmotherapy should not be implemented solely based on neuroradiological imaging and clinical examinations but on continuous bed-side ICP monitoring. Additionally, the existing data do not support the prophylactic administration of osmotherapy in patients with ischemic stroke without clear signs of brain edema or the administration in fixed intervals.

Hypothermia

Although the benefit of hypothermia has been shown in patients with recent resuscitation and in children with peripartal hypoxia, its clinical usefulness in ischemic stroke patients is still uncertain (61–64).Given the fact that fever is associated with worse outcome, the maintenance of normothermia is generally recommended in patients with intracranial mass effect due to stroke (65). However, this is not supported by randomized controlled trials (66).

Three of the most common ways to regulate body temperature in the critical care setting are via medication like non-steroidal anti-inflammatory drugs (for example paracetamol) or cold saline infusions, by surface cooling with ice bags or surface cooling systems (for example ArcticSun®) or by endovascular cooling systems (for example Thermoguard XP®) (67). Every cooling method has its distinctive advantages and disadvantes: whilst ice bags or cold saline infusions are easily available and inexpensive, maintaining the target temperature can be difficult. Furthermore, infusion of cold saline is limited in patients with cardiac failure due to possible hypervolemia. Surface cooling systems are easy to apply but can cause skin irritations and even cold burns. Intravenous cooling systems rely on semiautomatic body temperature control with electronic feedback. However, this goes with the risk of catheter infections and thrombosis.

As mentioned above, data on the benefit of hypothermia in stroke patients is scarce. One study, conducted before the RCTs on hemicraniectomy were published, followed the course of 36 patients with MMCAI of who 19 received moderate hypothermia of 33° whilst 17 patients underwent DC (68). The hypothermia group had a significantly higher mortality (12% in the DC group vs. 47% in the hypothermia group, respectively; $p = 0.02$). However, it should be noted that the patients in the hypothermia group did not receive DC. A recent study compared 53 retrospectively analyzed patients with MMCAI who would have fulfilled the inclusion criteria for the pooled analysis of randomized hemicraniectomy trials and were treated with DC and additional hypothermia (33–34°C) with 58 patients who underwent DC from the three European RCTs (DECIMAL, DESTINY, and HAMLET) (69). Hypothermia had no benefit on favorable functional outcome (mRS sores of 0–3) at 12 months (13/53 (25 %) vs. 24/58 (41%), aRR 0.66, 95%CI 0.38–1.13) but was associated with higher mortality (27/53 (51 %) vs. 46/58 (21%), RR 0.62, 95%CI 0.46–0.84 [results were basically unchanged after adjustement]) in this study.

Upcoming RCTs are investigating the benefit of hypothermia: Eurohyp is including patients with a NIHSS of 6 to 18, randomizing to best medical treatment or cooling for 24 h with a target temperature of 34–35°, either by surface or endovascular cooling systems (70). The trial is not directly aimed at patients

TABLE 3 | Recommendations for the treatment of patients with Malignat Middle Cerebral Artery Infarction after Decompressice Craniectomy [modified after (73)].

Clinical parameter	Recommendation
Airway and ventilation	Target pCO_2: 4.7 – 5.9 kPa; Target pO_2 > 8kPa; Target SpO_2 95–98%
Hemodynamics	Continuous monitoring of ECG and BP Monitor Treat cardiac arrhythmias, Avoid hypotension, tolerate initial transient hypertension Utilize isotonic fluid to maintain euvolemia. Target CPP 50–60 mmHg
Glucose target	Glucose 7.8 – 9.9 mmol/l (avoid hypoglycemia at all times)
Temperature	Maintain normothermia
Miscellaneous	Administer subcutaneous low-molecular-weight heparin for deep venous thrombosis prophylaxis or intermittent pneumatic compression No indication for seizure prophylaxis
Elevated ICP	Elevate head of bed to about 20-30°, keep neck straight to support venous return Start or increase analgesia and sedation Start mechanical ventilation Apply hyperventilation, but only short term Treat seizures, fever, hyperglycemia, respiratory distress, etc. if present Consider osmotherapy Consider barbiturates Consider muscle relaxation

BP indicates blood pressure; CPP, cerebral perfusion pressure; ECG, electrocardiography; kPa, kilopascal; ICP, intracranial pressure; pCO2, partial pressure of carbon dioxide; SpO2, peripheral oxygenated saturation.

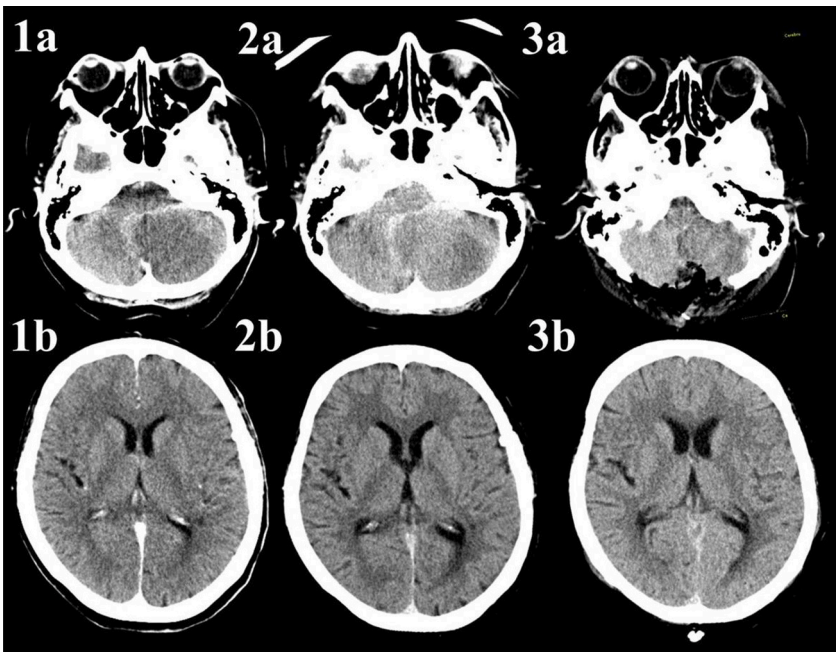

FIGURE 2 | Native CT-scans of a patient with infarction of the left posterior inferior cerebellar artery. The patient underwent no acute treatment due to late arrival and already visible ischemic changes. **Image 1a** shows the hypodense area on the left side of the cerebellum, there are no signs of cerebrospinal fluid circulation disturbance on **Image 1b**. **Image 2a** reveals progressive infratentorial edema with resulting enlargement on the ventricular system due to compression of the fourth ventricle (**Figure 2b**). **Images 3a**,**b** present a scan 1 day after suboccipital craniectomy. Whilst there is still enlargement of the frontal horns of both lateral ventricles, the third ventricle is slightly smaller, indicating flow restoration. The extraventricular drainage (EVD), implanted during the decompressive craniectomy, is not shown in these images.

with DC and is also suffering from slow recruitment with 98 of 1,500 planned patients enrolled until March 2018 (71).The results of the ***DE*compressive surgery *P*lus hypo*TH*ermia for *S*pace-*O*ccupying *S*troke** (**DEPTH-SOS**) trial that has randomized patients with MMCAI to cooling to 33°C ± 1 for 72 h in addition to DC are expected to be presented in November 2018 (72).

In view of the present evidence, hypothermia cannot be recommended in patients with MMCAI outside of clinical trials.

Summary of Special Care and Additional Therapy

Given the available evidence, apart from common critical care no definitive recommendation for additional therapies in patients with MMCAI who underwent DC can be given. Treating physicians may utilize certain measures to decrease elevated ICP based on individual decision making. However, one should be aware that none of these therapies are based on RCTs and are associated with possible side effects. An overview of the recommended medical management can be found in **Table 3** (73).

Posterior Circulation Stroke

About one fifth of all ischemic strokes are located in the posterior circulation and the diagnosis can be challenging due to non-specific symptoms like vertigo, nausea or reduced level of consciousness (74, 75). Large cerebellar infarction with subsequent mass effect followed by transforaminal brainstem herniation and hydrocephalus is the main target of surgical therapy in form of SOC in these patients (76, 77) (**Figure 2**). Although estimation of prognosis is difficult, patients with cerebellar infarction tend to have a more favorable outcome than patients with other stroke subtypes (78). However, it should be noted that data on long term outcome in these patients is scarce, and that additional ischaemia in adjacent territories like the brainstem and pre-existing conditions may significantly worsen the outcome (79). Large multicenter RCTs are lacking for this situation probably due to the well-known devastating effects of brainstem compression and hydrocephalus. In one of the largest trials, the German-Austrian Space-Occupying Cerebellar Infarction Study (GASCIS), 84 patients with massive cerebellar infarction were prospectively observed, with 34 (40%) receiving surgery, 14 (17%) receiving ventriculostomy and 36 (43%) receiving best medical treatment (80). The only predictor for poor outcome was reduced level of consciousness before treatment (OR 2.8, 95%CI 1.4–5.6). However, patients in GASCIS were not randomized, therefore causing a potential selection bias. Furthermore, 22.2% of patients initially treated with ventriculostomy also received SOC over the course of their hospital stay. Likewise with MMCAI, the timing of surgical therapy is paramount in patients with significant posterior fossa edema due to ischemic stroke (79). Whilst some authors argue that surgical therapy should be considered only when a significant decrease in the level of consciousness is present and that surgery in patients without coma is unproven, others tend

to treat more aggressively, as clinical signs or neuroradiological imaging of deterioration may be unspecific or detected too late (48, 81–83). Aggravating this situation is the fact that neuroradiological imaging in the posterior fossa is difficult: although dysfunction of cerebrospinal fluid circulation due to fourth ventricle compression by large cerebellar infarction may easily be spotted on plain CT, early ischemic changes in the posterior circulation can be missed due to bone artifacts (75). Additional test with MRI-DWI, CT angiography source images (CTA-SI) and CT-Perfusion (CTP) may facilitate detection of ischemic changes and estimation of overall outcome (84–86).

Concerning the extent of the surgical procedure, some authors argue that implantation of an extraventricular drainage (EVD) is sufficient, whilst others fear the possibility of upwards herniation across the tentorium (80, 87, 88). Although this question may not be sufficiently answered by current data, we recommend performing SOC with EVD implantation, with the possibility to extract the latter as early as possible if neuroradiological imaging shows sufficient cerebrospinal flow restoration after SOC (79).

In summary, SOC with or without insertion of EVD is an efficient procedure for the treatment of massive posterior fossa edema due to posterior circulation stroke. A strict age-dependent threshold whether to treat aggressively cannot be recommended. The decision to perform surgery should be made depending on pre-existing status of the patients and possible affection of other areas of the brain. As in MMCAI, data on the efficacy of additional therapies is scarce. Similar to MMCAI, we recommend utilizing these individually according to clinical status and neuroradiological imaging.

Ethical Considerations

Although there is sufficient evidence that DC in patients with MMCAI can be a lifesaving procedure, one should not forget that all patients who survive this condition will suffer from some form of disability. Although 43% of the patients in the pooled analysis of the three European RCTs achieved a mRS score of 0–3, only 7% patients in DESTINY II (i.e., patients older than 60 years) were able to walk without assistance (i.e., mRS score of 3) and no patient regained functional independence (i.e., mRS score of 2) (35, 38). In a recently published retrospective analysis of 66 patients in two tertiary stroke centers, 16% of patients aged 18–75 with DC after MMCI achieved functional independence (89).

The publication of the RCTs lead to an increase of DC in these patients, however, treatment decision making still is challenging as the survival can be at the cost of a life with severe disability, a fate often seen as unacceptable by patients (90, 91). Even if clinical and neuroradiological aspects lead to the recommendation for DC, surgery should only be performed after careful assessment of the patients' attitude toward the possibility of a life without the ability to care of their own bodily needs (43, 91, 92). Making the right decision in patients with MMCAI—whether performing aggressive surgical therapy with an uncertain outcome—represents the difficulty of applying population based study data and experience on individual patients. Further aspects of the ethical conflicts in these patients are discussed in another chapter of this article collection.

CONCLUSION

Malignant cerebral infarction is a life threatening condition with a mortality rate of 80% if treated conservatively. Decompressive craniectomy is the only therapeutic approach that is based on data of large randomized controlled trials in this condition. Decompressive craniectomy reduces the mortality rate in these patients, however leaving the majority of patients with at least some disability. Other treatment options like osmotherapy may be used in an individual risk-benefit-assessment, but evidence for these treatments and procedures is scarce. Before the surgical intervention, we recommend careful assessment of the patients' will.

AUTHOR CONTRIBUTIONS

L-PP wrote the manuscript. KB and VP were also involved in drafting the manuscript and revising it critically for important intellectual content.

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New or Blossoming Hemorrhagic Contusions After Decompressive Craniectomy in Traumatic Brain Injury: Analysis of Risk Factors

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Background: The development or expansion of a cerebral hemorrhagic contusion after decompressive craniectomy (DC) for traumatic brain injury (TBI) occurs commonly and it can result in an unfavorable outcome. However, risk factors predicting contusion expansion after DC are still uncertain. The aim of this study was to identify the factors associated with the growth or expansion of hemorrhagic contusion after DC in TBI. Then we evaluated the impact of contusion progression on outcome.

Methods: We collected the data of patients treated with DC for TBI in our Center. Then we analyzed the risk factors associated with the growth or expansion of a hemorrhagic contusion after DC.

Results: 182 patients (149 males and 41 females) were included in this study. Hemorrhagic contusions were detected on the initial CT scan or in the last CT scan before surgery in 103 out of 182 patients. New or blossoming hemorrhagic contusions were registered after DC in 47 patients out of 182 (25.82%). At multivariate analysis, only the presence of an acute subdural hematoma ($p = 0.0076$) and a total volume of contusions >20 cc before DC ($p = < 0.0001$) were significantly associated with blossoming contusions. The total volume of contusions before DC resulted to have higher accuracy and ability to predict postoperative blossoming of contusion with strong statistical significance rather than the presence of acute subdural hematoma (these risk factors presented respectively an area under the curve [AUC] of 0.896 vs. 0.595; $P < 0.001$). Patients with blossoming contusions presented an unfavorable outcome compared to patients without contusion progression ($p < 0.0185$).

Conclusions: The presence of an acute subdural hematoma was associated with an increasing rate of new or expanded hemorrhagic contusions after DC. The total volume of hemorrhagic contusions > 20 cc before surgery was an independent and extremely accurate predictive radiological sign of contusion blossoming in decompressed patients for severe TBI. After DC, the patients who develop new or expanding contusions presented an increased risk for unfavorable outcome.

Keywords: decompressive craniectomy, traumatic brain injury, hemorrhagic contusion, expansion of hemorrhagic contusions, acute subdural hematoma

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INTRODUCTION

The expansion of a cerebral hemorrhagic contusion after TBI occurs commonly and it is a widely studied phenomenon (1). Several series have reported a rate of progression of hemorrhagic contusions ranging approximately from 38 to 59% of cases (1, 2). In the last 20 years, the use of decompressive craniectomy (DC) for the treatment of uncontrollable high intracranial pressure (ICP) after TBI (3–11) has gradually increased. Indeed, the DC increases brain compliance and reduces ICP in presence of diffuse cerebral edema or intracranial hematomas (5–11). However, several authors reported that the change in pressure dynamics after DC can lead to the relief of the tamponade effect allowing the growth and/or progression of a hemorrhagic contusions (12–14).

A recent review about the complications of DC (12) reported a rate of expansion of hemorrhagic contusions after DC of 12.6% of adult patients and Flint et al. (14) have suggested that the occurrence of expansion of hemorrhagic contusions was associated with unfavorable outcome after DC. For these reasons, the recognition of risk factors associated with the growth or expansion of hemorrhagic contusion can improve the management of decompressed patients, identifying a subgroup of patients who might benefit from an early post-operative CT scan and from several potential therapeutic maneuvers minimizing hemorrhagic complications of DC.

However, few studies investigated factors associated with new or expanding contusions following DC. The aim of our study was to identify the risk factors associated with the growth or expansion of hemorrhagic contusion after DC in TBI. Then we evaluated the impact of contusion progression on outcome.

MATERIALS AND METHODS

We included in this retrospective study all patients treated with DC for TBI in our Department from January 2003 to December 2011.

The protocol of our Hospital for the management of severe TBI, which includes indication for DC, was based on current literature and on the Brain Trauma Foundation guidelines for management of intracranial pressure (ICP) following traumatic brain injury, fourth edition (3).

The management objectives are ICP $\leq$20–25 mmHg and cerebral perfusion pressure (CPP) $\geq$60 mmHg. ICP was monitored in unconscious patients with mass lesions potentially evolutive or edema with intraventricular drainage catheter or intraparenchymal probes. Patients with large epidural/subdural haematomas and contusions with significant mass effect underwent to surgery and in case of intraoperative massive brain swelling a primary decompressive craniectomy was performed. In the other patients, head elevation, sedation with propofol and analgesics infusion and mannitol were used to control ICP value. If these actions failed to control elevated ICP, thiopental infusion was started. Finally, DC was considered a last-tier treatment in case of persistent high ICP after barbiturates administration or adverse effects of thiopental. Usually we used an unilateral DC if there was a shift of the midline or one dilated pupil. Bifrontal DC were performed with the posterior limit at the coronal sutures. in patient with diffuse edema or bifrontal contusions.

Unilateral DC of at least 15 cm diameter were performed with the medial limit at least 2–2.5 cm lateral to the midline.

Bifrontal DC was performed with this technique in all cases: a large bicoronal incision was made and a large bifronto-temporal craniotomy was performed about 1–3 cm behind the coronal suture and including the bone over the superior sagittal sinus. Then anterior portion of the sagittal sinus is ligated and divided between the stitches and finally the falx was divided completely to achieve a maximal decompression.

All cases underwent expansive duraplasty with an allograft (lyophilized bovine pericardium).

From our analysis, we excluded patients with antiplatelet or warfarin use. Furthermore, all patients with coagulopathies already known before the trauma were excluded from the study. Data on blood tests on coagulation were not collected.

The primary study outcome focused on the development or expansion of a hemorrhagic contusion after DC.

Baseline characteristics (age, sex, cause of TBI, admission Glasgow Coma Scale score (GCS), admission pupils' reactivity, extracranial injury and Rotterdam score) DC were recorded and analyzed (**Table 1**).

All head CT scans performed by the patients included in this study were collected. The CT scans specifically evaluated for the purpose of this study were:

- the first CT scan on admission,
- the last CT scan achieved before DC (some patients performed only one CT scan before DC)
- the first CT scan performed after DC

Rotterdam score was calculated for each CT scan at admission. In each CT scan reported above we quantified the total volume and the side of each hemorrhagic contusions by measuring the ABC/2 volume (14) and summing the total hemorrhage volume of each contusion. We also evaluated the following variables on the initial head CT: cisternal effacement, midline shift $>$1 cm, subarachnoid hemorrhage, epidural hematoma, subdural hematoma, the number of hemorragic contusions pre-DC, and the total volume of contusions pre-DC.

Even surgical data including timing of DC and type of surgical approach (unilateral or bifrontal) were analyzed.

Finally, in the multivariate regression models the following variables were included:

- Age;
- GCS at admission;
- Pupils reactivity to the light;
- Timing of DC;
- Surgical approach (unilateral or bifrontal craniectomy);

Abbreviations: DC, decompressive craniectomy; TBI, traumatic brain injury; SAH, subarachnoid hemorrhage; GCS, glasgow coma scale; GOS, glasgow outcome scale; Gd, gadolinium; DTI, diffusion tensor imaging; SWI, susceptibility-weighted imaging; VEI, vessel-enhanced images; TEI, tissue-enhanced images; 3D PRESTO, three-dimensional principles of echo shifting with a train of observation; MinIP, minimum intensity projection; SWM, superficial white matter; DMV, deep medullary vein.

- State of cisterns;
- Midline shift;
- Presence of SAH;
- Rotterdam Score;
- The presence of Epidural Hematoma;
- The presence of Subdural Hematoma;
- Number of contusions;
- Total Volume of Contusions;

We also analyzed the number of patients who required a new surgery for the progression of hemorrhagic contusions and the clinical outcome (secondary end-point of the study) according to the presence or not of the development or expansion of a hemorrhagic contusion with the Glasgow Outcome Scale (5 point GOS) at 6-month follow-up. Death, persistent vegetative state and severe disability were considered as unfavorable outcome (GOS 1–3) while GOS 4–5 (good recovery and moderate disability) as favorable outcome. The mean follow-up period was 18 months (minimum 6 months–maximum 5 years).

Statistical Analyses

Data were analyzed with statistical package for social sciences (SPSS Inc., Chicago, Illinois, USA). Univariate analysis was performed by comparing patients who presented the growth or expansion of hemorrhagic contusion after DC in TBI and patients who did not. Continuous variables were compared using Student's *t* tests and Chi-square Test for discrete variables. The multiple logistic regression was used to identify independent risk factors. Power of the regression model to discriminate contusion progression was evaluated using receiver operating characteristic curve (ROC curves). Then a Pairwise *t* tests was used to compare the ROC curves. Statistical significance was set at $p < 0.05$.

RESULTS

The baseline characteristics of 190 patients treated with DC were summarized in **Table 1**.

TABLE 1 | Baseline characteristics of 190 patients with severe traumatic brain injury undergoing decompressive craniectomy.

Variabile	*N°*	(%)
Total number of patiens	190	
Mean age (years)	50	
Range	14–86	
SEX		
Male	115	(60.52%)
Female	75	(39.48%)
CAUSE OF TBI		
Road traffic accidents	111	(58.4%)
Falls	75	(39.6%)
Altro	4	(2%)
GCS AT ADMISSION		
3–5	129	(67.9%)
6–8	59	(31.1%)
>8	2	(1%)
PUPILS REACTIVITY TO THE LIGHT		
Yes	156	(82.1%)
No	34	(17.9%)
EXTRACRANIAL INJURY		
No	109	(57.4%)
Yes	81	(42.3%)
ROTTERDAM SCORE		
1–4	135	(71.05%)
5–6	55	(28.95%)

Among these 190 patients, eight patients did not have any postoperative head CT scan and they were excluded. Then, 182 patients (149 males and 41 females) were finally included in this study.

Hemorrhagic contusions were detected on the initial CT scan or in the last CT scan before surgery in 103 out of 182 patients (56.6%). Among these, 31 patients presented only one contusion while the remaining 72 patients suffered from multiple hemorrhagic contusions. The mean volume of contusions at the initial CT scan was 12.8 ± 2.7 cc.

After DC, new or blossoming hemorrhagic contusions were observed in 47 patients out of 182 (25.82%). Among these, 40 patients presented an expansion of the hemorrhagic contusion already depicted in pre-DC CT scan with a mean volume of 39.1 $\pm$ 3.1 cc, while 7 patients developed new hemorrhagic contusion with a mean volume of 28.3 $\pm$ 1.4 cc. Among these patients, 11 out of 47 (23.4%) required a new surgical intervention for uncontrollable ICP after DC or for the onset of one dilated pupil.

The results of univariate analysis were summarized in **Table 2**: age was not significantly associated with the progression or the growth of a contusion, while patients with new or blossoming contusion after DC presented a significantly lower GCS than those who did not ($p < 0.028$). No significant difference in pupils' reactivity to light, timing of DC and surgical approach (unilateral or bifrontal DC) were present between patients with or without blossoming of contusion. Among radiological data (presence of subarachnoid hemorrhage SAH, state of cistern, midline shift, presence of subdural or epidural hematoma and Rotterdam Score), only the presence of subdural hematoma was significantly associated with new or expanded hemorrhagic contusions at univariate analysis ($p = 0.027$). Finally, among the 103 patients with hemorrhagic contusions at pre-DC CT scan, the presence of multiple hemorrhagic contusions and a total volume of contusions <20 cc were significantly associated contusions progression (respectively $p = 0.043$ and $p < 0.0001$).

At multivariate analysis, only the presence of an acute subdural hematoma ($p = 0.0076$) and a total volume of contusions >20 cc before DC ($p = < 0.0001$) were significantly associated with expansion of hemorrhagic contusions (**Table 3**).

Then, power of the regression model to discriminate contusions progression was evaluated using ROC curves (**Figure 1**). The total volume of contusions before DC resulted to have higher accuracy and ability to predict postoperative blossoming of contusion with strong statistical significance rather than the presence of an acute subdural hematoma (these risk factors presented respectively an area under the curve [AUC] of 0.896 vs. 0.595; $P < 0.00$; **Table 4**).

TABLE 2 | Demographic, clinical, and imaging data for 182 patients included in statistical univariate analysis.

Variabile	Total *N°*(%)	Contusion Expansion after DC		
		Yes *N°*(%)	No *N°*(%)	*P*-Value
Total number of patiens	182	47 (25.82%)	135 (74.18%)	
Age (years)				0.944
<65 years	115 (63.2%)	29 (61.7%)	86 (63.7%)	
≥65 years	67 (36.8%)	18 (38.3%)	49 (36.3%)	
GCS at admission				**0.028**
3–5	126 (69.2%)	39 (82.9%)	87 (64.4%)	
6–8	56 (30.8%)	8 (17.1%)	48 (35.6%)	
Pupils reactivity to the light				0.578
Yes	148 (81.3%)	40 (85.1%)	108 (80%)	
No	34 (18.7%)	7 (14.9%)	27 (20%)	
Timing of DC				0.0771
<48 h	149 (81.9%)	43 (91.4%)	106 (78.5%)	
≥48 h	33 (18.1%)	4 (8.6%)	29 (21.5%)	
Surgical approach				0.981
Unilateral	145(79.7%)	38 (80.85%)	107 (79.25%)	
Bifrontal	37(20.3%)	9 (19.15%)	28 (20.75%)	
Cisterns				0.65
Compressed	149 (81.9%)	40 (85.1%)	109 (80.75%)	
Absent	33 (18.1%)	7 (14.9%)	26 (19.25%)	
Midline Shift				0.953
>10 mm	133 (73.1%)	34 (72.34%)	99 (73.33%)	
<10 mm	49 (26.9%)	14 (37.86%)	47 (26.77%)	
SAH				0.988
Yes	126 (69.2%)	33 (70.2%)	93 (68.8%)	
No	56 (30.8%)	14 (29.8%)	42 (31.2%)	
Rotterdam Score				0.947
1–4	98 (53.85%)	25 (53.1%)	73 (54%)	
5–6	84 (46.15%)	22 (46.9%)	62 (46%)	
Epidural Hematoma				0.96
Yes	17 (9.34%)	4 (8.5%)	13 (9.62%)	
No	165 (90.66%)	43 (91.5%)	122 (90.38%)	
Subdural Hematoma				**0.0188**
Yes	133 (73.1%)	41 (87.23%)	92 (68.14%)	
No	49 (26.9%)	6 (12.77%)	43 (31.86%)	
Number of contusions				**0.0436**
single	31 (30.1%)	12 (30%)	19 (30.15%)	
multiple	72 (69.9%)	28 (70%)	44 (69.85%)	
Total Volume of contusions				**< 0.0001**
<20 cc	68 (66.6%)	6 (15%)	62 (98.5 %)	
>20 cc	35 (33.4%)	34 (85%)	1 (1.5%)	

N°(%) = number of patients (percentage of patients). Bold Values are the values statistically significative.

Indeed, the volume of contusions presented significant higher sensibility (94.07%) and specificity (85.11%) compared with the presence of acute subdural hematoma (respectively 31.85 and 87.23; **Figures 2**, **3**).

Finally, the patients with blossoming hemorrhagic contusions after DC presented higher risk of unfavorable outcome compared with patients with no or stable contusions ($p < 0.0185$; **Table 5**).

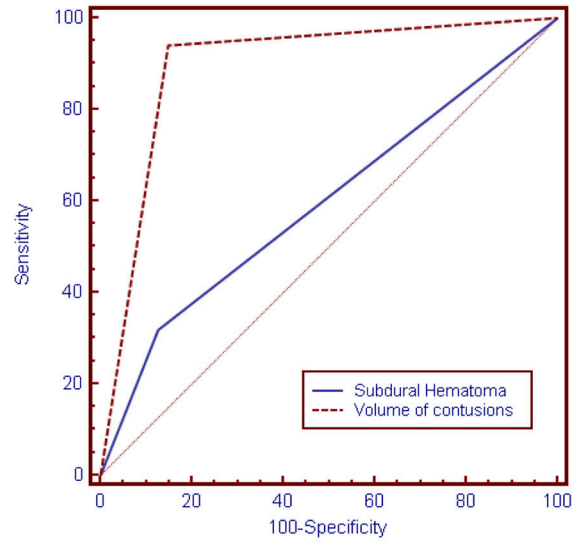
DISCUSSION

Recent literature, including several retrospective studies and two recent randomized controlled trials (1–11), reported that while DC is able to reduce ICP and mortality of patients with uncontrollable ICP after TBI, on the other hand, it leads to an increase of patients with severe disability (1–11).

TABLE 3 | Multiple logistic regression model after variable selection (data is based on CT-scans before DC).

Variable	OR	95% CI	Coefficient	Standard Error	*P*-Value
GCS at admission	1.9238	0.2537 to 14.5865	0.6543	1.0336	0.5267
Number of contusions	0.3144	0.3144 to 29.8745	−1.1572	1.0568	0.2735
Subdural Hematoma	**29.7859**	**2.4677 to 359.5208**	3.3940	1.2708	**0.0076**
Total Volume of contusions	**0.0012**	**0.0001 to 0.0112**	−6.7661	1.1624	**<0.0001**

Bold Values are the values statistically significative.



	AUC	SE	95% CI
Subdural_Hematoma	0,595	0,046	0,520 to 0,667
Volume_of_contusions	0,896	0,032	0,842 to 0,936

Pairwise comparison of ROC curves

Subdural_Hematoma ~ Volume_of_contusions	
Difference between areas	0,300
Standard error	0,054
95% Confidence interval	0,195 to 0,406
Significance level	P < 0,001

FIGURE 1 | ROC curves analysis.

TABLE 4 | ROC curves analysis for comparing the accuracy of the presence of subdural hematoma or pre-DC total volume of contusions in predicting contusion expansion after DC.

Variable	AUC	SE	95% CI
Subdural Hematoma	0.595	0.046	0.52 to 0.667
Total Volume of contusions	0.896	0.032	0.842 to 0.936
PAIRWISE COMPARISON OF ROC CURVES			
Difference between area			0.300
SE			0.054
95% CI			0.195 to 0.406
Significance level			$P < 0.001$

ROC, Receiver Operating Characteristic; AUC, Area Under the Curve; SE, Standard Error; CI, Confindence Interval.

This data is related also to the high rate of complications secondary to DC (including hemorrhagic complications, infectious complications and disturbances of the CSF compartment) greater than any other neurosurgical intervention (12–22). The growth or expansion of hemorrhagic contusion is one of the main complications of DC after TBI (12–15).

For this reason, the identification of risk factors associated with new or worsened cerebral hemorrhage after DC is important in order to optimize diagnostic and management strategies. However, while the incidence and risk factors for blossoming contusions after TBI has been extensively analyzed, the same phenomenon following DC have not been thoroughly investigated (2, 12–15).

In a recent review about the complications of DC (12), the overall rate of "hemorrhagic complications" in TBI (including new or progression of epidural, subdural or intracerebral hemorrhage) was 11.9% and was secondary only to CSF disturbances (18.4%). Moreover, in this review hemorrhagic progression of a contusion was observed in 12.6% (163/1256) of TBI patients treated with DC. These authors reported that new and expanding hematomas occur early after DC, and they suggested as possible cause the loss of the tamponading effect of high ICP (12–14).

In our series, the rate of growth or expansion of hemorrhagic contusion after DC was higher than in the above-mentioned review (25.82 vs. 12.6%). However, this review (12) did not report the definition of each study included about the hemorrhagic contusion progression and this issue may underestimate the real incidence of this complication.

In this regard, Flint et al. (14) reported new or expanded hemorrhagic contusions $\geq$ 5 cc after DC in 23 patients out of 40 (58%).

Hemorrhagic contusion expansion was closely linked to the injury process after TBI and in previous studies it was observed in 42% of 142 TBI patients with median GCS scores of 8 and in 47% of 141 patients with traumatic subarachnoid hemorrhage (1, 2, 13). Furthermore, several studies identified DC as risk factor for contusion progression after TBI (23).

However, the real impact of DC on contusion expansion and the pathophysiology has not been clearly investigated in literature (12–15).

In a recently experimental animal model (about the effect of DC in a murine model of head injury), DC increases the devolvement of brain edema and contusions expansion (24). The

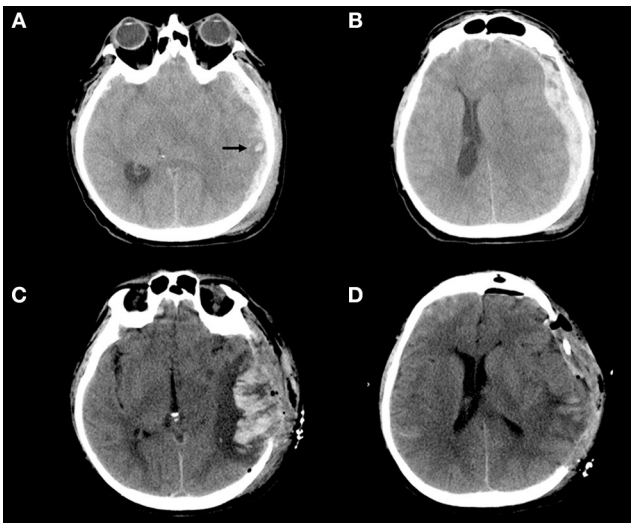


FIGURE 2 | (A–D) Example of blossoming contusion in a 52-year-old male patient treated with DC for traumatic acute subdural hematoma. The patient sustained a close head injury in a motor vehicle accident and 2 h after trauma was admitted at our hospital with a Glasgow Coma Scale score of 6 (E1V1M4) and was put under mechanical ventilation. The pupils were bilaterally equal and reactive. **(A,B)** (Pre-operative CT scan). Pre-operative CT scan, immediately performed after admission of the patient described above, showing a large left acute subdural hematoma with a small temporal contusion [black arrow–**(A)**] and midline shift **(B)**; then the patient was immediately operated. **(C,D)** (Post-operative CT scan) Post-operative CT scan performed about 3 h after DC demonstrating massive contusion expansion **(C)** after wide DC **(D)**. During surgery bone flap was not replaced for massive brain swelling without evidence of bleeding/contusion enlargement at the level of temporal lobe.

authors postulated, as a possible pathophysiological explanation, that in their model a mechanic relief of tamponade effect due to DC may favor further increase of intracerebral bleeding with the beginning of vicious circle characterized by peri-hemorrage edema and secondary ischemic-hemorrhagic changes.

The main goal of this study was to identify the risk factors associated with the growth or expansion of hemorrhagic contusion after DC in TBI with the aim to identify a subgroup of decompressed who may benefit from closer CT monitoring and targeted therapies aimed at reducing intracranial bleeding.

Previous studies (14, 15) reported that the value of Rotterdam score, a radiological measure of TBI severity on the first CT scan, was associated with the blossoming contusions after DC. Flint et al. (14) reported that patients with Rotterdam scores 5 or 6 had an 78,6% (11/14) chance of expansion of their hemorrhagic contusions after DC.

On the contrary, in our study the Rotterdam score was not statistically associated with the growth or progression of the hemorrhagic contusion. Instead, in our series, the only radiological variable independently associated with increased risk of blossoming contusion was the presence of an acute subdural hematoma ($p = 0.0076$). In previous studies about contusion progression after DC this association was not found, however several papers focused on the natural history of brain contusion reported an independent association between acute subdural hematoma and contusion blossoming (24, 25). Alahmadi et al. (25) suggested (as possible explanation) that some acute subdural hematoma might be secondary to a burst lobe from an underlying large contusion that was more likely to enlarge.

Furthermore, Wang et al. (15) presented in their prediction model of the risk factors of hemorrhagic contusions a clear relationship between increased hemorrhage volumes and GCS score. This data was not confirmed by our study in where GCS score was similar in patients with and without hemorrhage expansion after DC.

The second factor in our study independently related to the development of new contusion or expansion of intracerebral post-traumatic hemorrhage, was the initial volume of brain contusion. Thirty Four patients out of 35 (97%) with a total hemorrhage volume $>$ 20 cc at pre-DC CT scan presented expansion of contusion.

Neither Wang (15) nor Flint (14) have analyzed in their studies the association between the total volume of contusions before DC and the rate of progression of the contusions themselves. While in other studies about the natural history of post-traumatic hemorrhagic contusion among all baseline variables, the initial contusion volume represents the more accurate prognostic factor (2, 24). Several studies reported that the initial volume of hemorrhagic contusion was proportionally related to the rate of hemorrhagic progression, with smaller lesions remaining relatively stable and larger ones more likely to enlarge (24).

In our series, we evaluated the power of each independent variable at the regression model using ROC curves. The total volume of contusions resulted to have higher accuracy and ability to predict postoperative blossoming of contusion with strong statistical significance rather than the presence of acute subdural hematoma (these risk factors presented respectively an area under the curve [AUC] of 0.896 vs. 0.595; $P < 0.001$).

Indeed, the pre-DC total volume of contusions presented significant higher sensibility (94.07%) and specificity (85.11%) compared with the presence of acute subdural hematoma (respectively, 31.85 and 87.23%).

Finally, patients with new or expansion of hemorrhagic contusions after DC presented an increased risk for poor outcome ($p < 0.0185$).

The main limitations of this study included:

- The association between contusion blossoming and unfavorable outcomes at 6-month follow- up may be most likely due to their association with more severe primary brain injury and did not necessarily confirm a cause-and-effect relationship. Indeed, because the indication to DC was essentially based on clinical conditions, patients with the most severe TBI were those likely treated with DC.
- Another important issue is the eventuality that a significant rate of hemorrhagic contusion expansion might have occurred after the last pre-operative CT scan but before DC. This factor inserts a source of bias: it is not possible in fact to exclude in our study that a significant part of the hemorragic contusions evolved before the DC

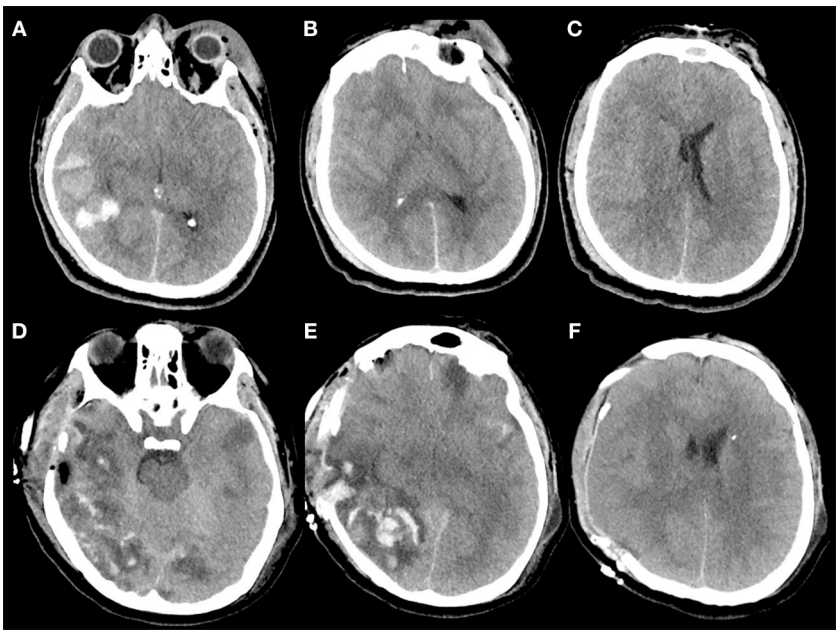


FIGURE 3 | (A–F) Example of contusion expansion in a 35-year-old patient who underwent to DC for uncontrollable high ICP secondary to brain swelling and temporal hemorrhagic contusion with total volume > 20 cc. The patient sustained a polytrauma with TBI after intentional precipitation and 3 h after trauma was admitted at our hospital with a Glasgow Coma Scale score of 4 (E1V1M2) and was put under mechanical ventilation. The pupils were bilaterally equal and reactive. **(A–C)** (Pre-operative CT scan) Pre-operative CT scan, immediately performed after admission of the patient described above, showing a right temporal post-traumatic hemorrage with total volume > 20 cc **(A)**, diffuse brain swelling **(B)**, and left midline shift **(C)**; after this CT, an intraparenchymal probe for ICP monitoring was placed on the right side with stable values of ICP up to 30 mm Hg despite maximal medical treatment. Then the patient was immediately operated and a right DC was performed. During surgery, no active bleeding was observed at the level of temporal contusion and for this reason no lobectomy was performed. **(D–F)** (Post-operative CT scan) Post-operative CT scan performed 1 h after surgery demonstrating massive contusion expansion **(D,E)** and initial herniation of the brain away from the craniectomy defect **(F)**.

TABLE 5 | Outcome at 6-months follow-up of patients undergoing DC after severe TBI categorized by the presence or not of new or expansion of hemorrhagic contusion.

Outcome	Total	Expansion of hemorrhagic contusions		*P*-Value
		Yes	No	
Unfavorable (GOS 1-3)	124 (68.2%)	39 (82.98 %)	85 (62.9%)	**<0.0185**
Favorable (GOS 4-5)	58 (31.8%)	8 (17.02%)	50 (37.1%)	

Bold Values are the values statistically significative.

- From our analysis, we excluded patients with antiplatelet or warfarin use or patients with coagulopathies already known before the trauma were excluded from the study. Data on blood tests on coagulation were not collected. This is fact involves another possible bias: we cannot exclude in our series that several blossoming contusions could be due to unknown coagulation disorders
- A mean of 5 CTs scans were performed for patient. Unfortunately, CT scans were not all analyzed on the same day of follow-up after DC; but they were analyzed as first, second and third CT after DC for each patient. This limitation may underestimate the effect of DC on the expansion of contusion in patients with early CT scan after surgery compared with patients with late CT scan.
- Finally, the manipulation of swollen and contused brain during the evacuation of acute subdural hematomas (ASDH) may lead in some cases to the development of new contusions or to the expansion of pre-existent traumatic intraparenchymal hemorrhage. Therefore, in our study the expansion of a part of contusions after ASDH evacuation could be secondary to a direct surgical complication rather than to an effect of the DC itself.

CONCLUSIONS

The presence of an acute subdural hematoma was associated with an increasing rate of new or expanded hemorrhagic contusions after DC. The total volume of hemorrhagic contusions >20 cc before surgery was an independent and extremely accurate predictive sign of contusion blossoming in decompressed patients for severe TBI. Patients with blossoming contusions after DC presented an increased risk for unfavorable outcome.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of name of guidelines, name of committee with written informed consent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the name of committee.

AUTHOR CONTRIBUTIONS

DN: design of the work, analysis and interpretation of data for the work, and drafting the work. LdS: acquisition, analysis, and interpretation of data for the work. MG: acquisition, analysis, and interpretation of data for the work. EM: design of the work, acquisition, and interpretation of data for the work. MS: design of the work and revising the work critically. MI: interpretation of data for the work, and revising the work critically. MD: design of the work, drafting the work and revising the work critically. All authors: final approval for publication of the content, and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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REVIEW
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Timing of Decompressive Craniectomy for Ischemic Stroke and Traumatic Brain Injury: A Review

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While studies have demonstrated that decompressive craniectomy after stroke or TBI improves mortality, there is much controversy regarding when decompressive craniectomy is optimally performed. The goal of this paper is to synthesize the data regarding timing of craniectomy for malignant stroke and traumatic brain injury (TBI) based on studied time windows and clinical correlates of herniation. In stroke patients, evidence supports that early decompression performed within 24 h or before clinical signs of herniation may improve overall mortality and functional outcomes. In adult TBI patients, published results demonstrate that early decompressive craniectomy within 24 h of injury may reduce mortality and improve functional outcomes when compared to late decompressive craniectomy. In contrast to the stroke data, preliminary TBI data have demonstrated that decompressive craniectomy after radiographic signs of herniation may still lead to improved functional outcomes compared to medical management. In pediatric TBI patients, there is also evidence for better functional outcomes when treated with decompressive craniectomy, regardless of timing. More high quality data are needed, particularly that which incorporates a broader set of metrics into decision-making surrounding cranial decompression. In particular, advanced neuromonitoring and imaging technologies may be useful adjuncts in determining the optimal time for decompression in appropriate patients.

Keywords: TBI, stroke, decompressive hemicraniectomy, timing, herniation

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INTRODUCTION

Decompressive craniectomy has been used to treat elevated intracranial pressure (ICP) resulting from various etiologies, especially ischemic and traumatic brain injuries. Given the inflexible confines of the skull, brain swelling from stroke or TBI can result in a compartment syndrome, increasing intracranial pressure (ICP). This can reduce cerebral perfusion pressure (CPP), cerebral blood flow (CBF), and oxygenation (1). If not acted upon, this can lead to brain ischemia, infarction, herniation, and death. There are various management strategies to treat elevated ICPs which include sedation, hyperventilation, hyperosmolar therapy, paralysis, hypothermia, barbiturates, and cerebrospinal fluid drainage (2). Decompressive craniectomy is a treatment option generally reserved for ICP elevation refractory to less invasive treatments (3).

Although decompressive craniectomy has been shown to effectively reduce ICP (4), there remains much controversy regarding its effect on overall clinical outcome, especially following TBI (5). Additionally, it is becoming clear that factors such as timing of decompressive craniectomy may

play a significant role in determining the therapeutic benefit of this procedure. There are various studies providing insight into the optimal timing of decompressive craniectomy for victims of TBI and ischemic stroke and it is important for neurosurgeons to be aware of this data. The goal of this paper is to synthesize published findings regarding optimal timing for craniectomy for both malignant stroke and TBI in relation to time from injury and in relation to cerebral herniation.

TIMING OF CRANIECTOMY AFTER ISCHEMIC STROKE

Decompressive Craniectomy for Stroke in the Animal Model

Some animal data have suggested that early decompressive craniectomy could yield better functional outcomes than late decompression or non-operative management. In two animal studies with standardized experimental conditions, rats undergoing decompressive craniectomy after MCA infarction had a significantly better outcome and had a reduction in infarct size when compared to the non-surgical groups (6, 7). These studies were based on the hypothesis that avoiding herniation and mesencephalic ischemia would improve prognosis. Doerfler et al. concluded that the decompressive craniectomy groups demonstrated better mortality and neurologic outcome when compared to the non-surgical group (6). It was further concluded that the animals treated with very early decompression (within 4 h) demonstrated significantly better neurologic outcomes and smaller infarct size compared to animals treated with later decompression. Forsting et al. also found that decompressive craniectomy improved outcomes, mortality, and infarct size when compared to the non-surgical group regardless of when the decompression occurred (7).

Decompressive Craniectomy Within 48 h of Ischemic Stroke

Decompressive craniectomy following acute ischemic stroke has been studied in three relatively recent human randomized controlled trials. These studies analyzed the effects of decompressive surgery on mortality and functional outcome after malignant hemispheric stroke. The subsequent pooling and meta-analysis of these studies has generated very important insights as will be described.

DECIMAL (Decompressive Craniectomy in Malignant Middle Cerebral Artery Infarcts) was published in 2007. It assigned 38 patients to undergo surgery or medical management within 30 h of their initial stroke (8) (see **Table 1**). When compared to the medical therapy cohort, the cohort that underwent decompressive craniectomy demonstrated a mortality rate that was more than halved, and a 50% increase in the proportion of patients with only moderate disability.

DESTINY (Decompressive Surgery for the Treatment of Malignant Infarction of the Middle Cerebral Artery) was also published in 2007. It enrolled 32 patients within 36 h of stroke (9). This randomized study demonstrated that craniectomy reduces mortality in large hemispheric stroke. Like DECIMAL, this study demonstrated a reduction in death rates in the surgical cohort, but also like DECIMAL the sample size of the DESTINY trial was not sufficient to draw conclusions regarding functional outcome.

Because the above studies were underpowered to assess differences in functional outcomes, the HAMLET (Hemicraniectomy After MCA Infarction With Life Threatening Edema Trial) trial was initiated. This third RCT was published in 2009 and was crucial in adding to the body of literature regarding decompressive surgery following acute ischemic stroke (10). HAMLET enrolled 64 patients up to 96 h after stroke. This RCT demonstrated that when decompressive craniectomy is delayed up to 96 h, there was no improvement in functional outcomes in survivors. The percentage of patients with a mRS score less than or equal to three at 1 year follow up were comparable between the decompressive craniectomy and control group (25% in both groups). It should be noted that three patients in the surgical group and three patients in the medical group had a fixed and dilated pupil on enrollment which means that roughly 20% of the study population demonstrated signs of herniation prior to treatment. Because 20% of this study population had already demonstrated signs of herniation, it can be argued that delayed craniectomy may be too late to impart any functional benefit.

A meta-analysis of the three studies was performed by Vahedi et al. on the patients treated with surgery within 48 h in the DECIMAL and DESTINY trials as well as the first 23 patients of the HAMLET trial (11). In this meta-analysis of 93 patients crossover was minimal: there was only one crossover from non-operative treatment to decompressive surgery included in this analysis from the DESTINY trial. The results demonstrated increased favorable functional outcome compared to the medical cohort (11). In this paper, 43% of the decompressive craniectomy group had a modified Rankin scale (mRS) score of 0–3 compared to 21% in the control group. It should be noted that from the human studies presented thus far, there have been no direct comparisons between outcomes of early vs. late decompressive craniectomy.

The findings from the meta-analysis performed by Vahedi et al. was further corroborated by the findings of Vibbert et al. This study contained 64 patients with acute ischemic stroke in the MCA territory who presented within 96 h of symptom onset. The patients were randomized to receive medical management or surgical intervention (3). The primary outcome was the modified Rankin scale (mRS) at 12 months which was stratified as good outcome (0–3) and severe disability or death (4–6). Twenty-four out of 32 patients in each arm had a mRS score >3 at 12 months, and rates of severe disability were also similar between groups. The risk of death was significantly reduced in the surgical group (absolute risk reduction of 38%; $P = 0.002$). The authors performed subgroup analyses of patients who underwent surgery in <48 h and patients who underwent surgery after 48 h. For patients who underwent surgery within 48 h of stroke, the risk of death and an mRS score >4 were reduced (respectively: ARR, 59%; 95% CI, 33–84; ARR 30%; 95% CI, 1–59) (3).

Vibbert et al. then performed an updated meta-analysis with their cohort of patients and patients from the aforementioned DECIMAL, DESTINY, and HAMLET trials who underwent decompressive surgery within 48 h (3). Corroborating their prior

TABLE 1 | Decompressive craniectomy for stroke studies.

	Author	Study design	Patients	Selection criteria	Treatment	Total no of patients	Time to DC	Mortality *n*(%)	Functional outcome at 6 months	Functional outcome at 12 months	Conclusions
Stroke	Vahedi et al. (8)	Randomized controlled trial	Adult patients with MCA infarction	Patient age 18–55 years, within 24 h of a malignant MCA infarction, NIHSS ≥ 16,; >50% of the MCA territory involved on CT; DWI infarct volume >145 cm^3	DC	20	Avg 20.5 ± 8.3 h (range, 7–43 h)	5 (25)	mRS score ≤3: 25%	mRS score ≤3: 50%	When compared to medical management, the DC group demonstrated an increase in the number of patients with moderate disability by more than half and demonstrated a reduction in the mortality rate by more than half.
					Medical management	18	NA	14 (78)	mRS score ≤3: 5.6%	mRS score ≤3: 22.2%	
	Juttler et al. (9)	Randomized controlled trial	Adult patients with MCA infarction	Patient age 18–60 years, at least 2/3 of MCA territory infarction with basal ganglia involvement, NIHSS >18 for non-dominant hemisphere, NIHSS > 16 for dominant hemisphere, symptoms > 12 h but <36 h before possible DC	DC	17	Within 36 h after stroke	2 (11.8)	mRS score ≤3: 47%	mRS score ≤3: 47%	DC reduces mortality in large hemispheric stroke. Functional outcomes at 6 and 12 months were comparable between both groups
					Medical management	15	NA	8 (53.3)	mRS score ≤3: 27%	mRS score ≤3: 27%	
	Hofmeijer et al. (10)	Randomized controlled trial	Adult patients with MCA infarction	Patient age 18–60, at least 2/3 of MCA territory stroke within 96 h of treatment, NIHSS score >16 right sided lesions or >21 left sided lesions,	DC	32	Within 96 h after stroke	7 (22)	NA	mRS score ≤3:25%	DC can improve fatality and functional outcomes when performed within 48 h; however, when delayed up to 96 h, there was no improvement in functional outcomes.
					Medical management	32		19(59)	NA	mRS score ≤3:25%	
	Vibbert et al. (3)	Randomized controlled trial	Adult patients with MCA infarction	Patient age 18–60, at least 2/3 of MCA territory stroke within 96 h of treatment, NIHSS score >16 right sided lesions or >21 left sided lesions,	DC	32	Within 96 h after stroke	NA	NA	mRS score ≤3:25%	DC can improve fatality (absolute risk reduction of 38%); however, there was no improvement in functional outcomes.
					Medical management	32		NA	NA	mRS score ≤3:25%	
	Schwab et al. (12)	Prospective cohort	Adult patients with MCA infarction	Patients younger than 70, >50% MCA territory infarction noted on CT imaging	Early DC	31	Within 24 h after stroke	5 (16)	Avg Barthel Index Score: 68.8	NA	Earlier DC was associated with lower mortality. There was a trend toward better functional outcomes, and the patients spent less time in the ICU

(Continued)

TABLE 1 | Continued

Author	Study design	Patients	Selection criteria	Treatment	Total no of patients	Time to DC	Mortality *n*(%)	Functional outcome at 6 months	Functional outcome at 12 months	Conclusions
				Late DC	32	>24 h after stroke	11 (34.4)	Avg Barthel Index Score: 62.6	NA	
				Medical management	55		43 (78)	Avg Barthel Index Score: 60	NA	
Wang et al. (13)	Retrospective cohort	Adult patients with MCA infarction	Patients with 1st stroke >90% MCA infarction	Early DC	11	Within 24 h after stroke	3 (27)	Mean Glasgow Outcome Score: 2.5	NA	While the mortality rates were comparable between groups, severe disability may be reduced in early treated patients
				Late DC	10	>24 h after stroke	3 (30)	Mean Glasgow Outcome Score: 2.45	NA	
				Medical management	41		9 (22)	Mean Glasgow Outcome Score: 2.73	NA	
Cho et al. (14)	Retrospective cohort	Adult patients with MCA infarction	Patients with > 50% MCA infarction with NIHSS score > 20	Ultra-early DC	12	Within 6 h after stroke	1 (8.3)	Avg Barthel Index Score: 70	NA	DC before neurologic compromise may reduce the mortality rate and increase the conscious recovery rate
				Delayed DC	30	>6 h after stroke	11 (36.7)	Avg Barthel Index Score: 52.9	NA	
				Medical management	10		8 (80)	Avg Barthel Index Score: 55	NA	
Mori et al. (15)	Retrospective cohort	Adult patients with MCA infarction	Patients <85 years of age with patients with embolic hemispheric infarction volume > than 200 cm3	Early DC	21	DC before brain herniation	4 (19.1)	Avg Barthel Index Score: 52.9	NA	Early DC before the onset of brain herniation should be performed to improve mortality and functional recovery. DC after signs of herniation may be too late for functional benefit
				Late DC	29	DC after brain herniation	8 (27.6)	Avg Barthel Index Score: 26.9	NA	
				Medical management	21		15 (71.4)	Avg Barthel Index Score: 28.3	NA	
Elsawaf et al. (16)	Prospective cohort	Adult patients with MCA infarction	Patients with malignant MCA infarction	DC based on clinical status	27	DC with deterioration of consciousness	14 (52)	Mean mRS Score: 4.7	NA	Early prophylactic DC yields better clinical and radiographic outcomes than DC based on clinical status
				Early DC	19	DC within 6 h of stroke	2 (10.5)	Mean mRS Score: 3.5	NA	

findings, the data suggest a significant reduction in risk of death (ARR, 49.9%; 95% CI, 33.9–65.9) and in the risk of severe disability at 12-months (ARR, 41.9%; 95% CI, 25.2–58.6). While not statistically significant, there was a notable trend toward reduction in risk of poor outcome (12 month mRS score >3—ARR, 16.3%; 95% CI, −0.1–33.1).

In summary, decompressive craniectomy within 96 h of malignant MCA stroke did not reduce poor outcomes at 1 year; however, there seems to be a trend toward reduction in death and moderate-to-severe disability (mRS score>4) when surgery was performed within 48 h from the stroke. It is possible that a significant portion of patients 96 h from an acute ischemic stroke may already exhibit herniation, and decompressive craniectomy at this time may be too late to impart functional benefit. Unfortunately, analysis of outcome in relation to herniation events was insufficiently described in these studies, and it is not possible to determine whether early surgery is beneficial due to avoiding herniation or whether there is a benefit to early surgery independent of herniation. The benefit of early surgery in the cohort by Vibbert et al. was not as great in magnitude as in HAMLET; however, this may have been due to a longer interval between symptom onset and surgical treatment in HAMLET (mean 31 h) than in DECIMAL (mean 16 h) and DESTINY (mean 24 h).

Decompressive Craniectomy Within 24 h of Ischemic Stroke

Other data have suggested that early decompressive craniectomy within 24 h of stroke could yield even better functional outcomes. Schwab et al. conducted a prospective observational trial where the patient population was stratified by early craniectomy (<24 h after symptom onset) and late craniectomy (>24 h), with additional comparison to a natural history group (12). Patients were included in the study if they had >50% MCA territory infarction noted on CT imaging. The mean time between symptoms and surgery was 21 h (range, 8–42 h) in the early craniectomy group and 39 h (range, 6–112 h) in the late group. This difference approached statistical significance ($p = 0.07$). Mortality was 16% (5/31) in the early group, 34.4% (11/32) in the late group, and 78% (43/55) in the historical controls (12). The late group demonstrated uncal herniation in 24 of 32 patients (75%) whereas only 4 of 31 patients (13%) in the early group demonstrated uncal herniation. Length of stay in the ICU was 7.4 days for the early group and 13.3 days in the late treated group ($p = 0.05$). Functional outcome measured by the Barthel Index (BI) demonstrated a higher mean score for the early group with an average score of 70 vs. 62.6 in the late group. There was a trend toward better outcomes with early craniectomy, however, the data were not statistically significant. Overall, this study demonstrated that early craniectomy was an efficacious approach for treating malignant MCA infarction when the patients were treated before signs of herniation. The mortality rate was lower, there was a trend to better functional outcome, and the patients spent less time in the ICU.

The data presented by Schwab et al. were further corroborated by smaller series published by Wang et al. and Cho et al. In a retrospective study of 21 patients, Wang et al. compared the outcomes of early decompression (<24 h) to late decompression (>24 h) (13). While the mortality rate was comparable, Wang et al. demonstrated that severe disability may be reduced in early treated patients. Cho et al. further corroborated this data, and demonstrated the positive results in association with ultra-early decompression defined as decompression within 6 h of symptom presentation (14). The Cho et al. study reported only a cohort of 52 patients and demonstrated that the acute mortality rate was statistically lower for the ultra-early group (8.3%) compared to the delayed decompression group (>6 h) and the no surgery group (36.7 and 80%, respectively, all p-values < 0.001). The ultra-early group also had better prognosis for conscious recovery (91.7%) compared to the delayed decompression group and the no surgery group (55 and 0%, respectively). While more data are needed, the published data give credence to the idea that early craniectomy performed within 24 h yields better mortality and functional outcomes. Moreover, this study suggests that the benefit to early surgery may not merely stem from an avoidance of herniation.

Decompressive Craniectomy for Ischemic Stroke Based on Clinical Correlates of Herniation

While the previous studies demonstrated benefit from early decompression, a key limitation was insufficient delineation of the role of herniation events in distinction to merely performing early surgery. Indeed, there have been more recent studies that indicate that the timing of craniectomy should be based on clinical features rather than on a strict temporal scale given the variations in when herniation events occur in the clinical course of different patients. A retrospective study by Mori et al. analyzed the outcomes of 71 patients with embolic hemispheric infarctions (infarct volume >200 cm^3) who were stratified into 3 groups: non-operative management, decompressive craniectomy after brain herniation (late surgery group), and decompressive craniectomy before brain herniation (early surgery group) (15). This study utilized the Glasgow Coma Scale (GCS), changes in mental status, and anisocoria as clinical indicators for herniation. The mortality at 1 and 6 months in the non-operative group was 61.9 and 71.4%, respectively. The mortality at 1 and 6 months in the late surgery group was 17.2 and 27.6%, respectively, ($p = 0.01$) and was even better in the early surgery group −4.8 and 19.1%, respectively. The Glasgow Outcome Scale (GOS) and Barthel Index (BI) were employed as functional outcome measures at 6 months. The GOS scores of the early surgery group were better than those of the late surgery group ($p = 0.05$). The average BI score of the early surgery group (52.9 ± 34.2) were improved from those of the late surgery group (26.9 ± 30.4) ($p = 0.05$). The late surgery group had a comparable BI score to the non-operative group (28.3 ± 42.2), which indicates that surgery after signs of herniation may be too late to yield functional benefit. Mori et al. thus concluded that an effort should be made to perform early decompressive craniectomy before the onset of

brain herniation in patients with malignant cerebral infarction. Mori et al. also concluded that embolic stroke patients with >200 cm^3 volume of infarction and shift of the midline structures on a follow-up CT 2 days after ictus are more likely to herniate and would benefit from decompressive craniectomy.

Mori et al. advanced the field by conceptualizing outcome in relation to clinical indicators of herniation. With this in mind, Elsawaf et al. published a recent and important prospective study comparing outcomes of early decompression (within 6 h of presentation) and decompression based on clinical features of deterioration. Forty-six patients with large hemispheric MCA infarction were divided randomly into two groups: Group I in which patients were followed until deterioration of level of consciousness, and Group II in which patients were operated within 6 h of presentation regardless of clinical signs of deterioration or radiographic features (16). While both groups demonstrated improvement in conscious level, motor power, and functional outcome, there was significant improvement ($p < 0.05$) in functional outcome in group II based on the mRS. Group I demonstrated increased progression of infarct volume when compared to Group II, and also had a morality of 52% due to delay in surgery compared to 10% in Group II. This study found better clinical and radiographic outcomes for patients with large hemispheric MCA infarction who were operated on prophylactically within 6 h of infarction without waiting for deterioration of level of consciousness.

While there are concerns that very early decompression surgery might potentially be unnecessary, the presented data demonstrate that decompression after the onset of herniation symptoms is less effective, or may even be ineffective in reducing mortality and improving neurological outcome. While more data are required, current studies suggest that stroke patients with malignant infarction >200 cm^3 and follow up CT at 2 days from symptom onset which demonstrate shift of the midline structures are likely to herniate and would benefit from early decompressive craniectomy.

TIMING OF CRANIECTOMY AFTER TRAUMATIC BRAIN INJURY

Decompressive Craniectomy for Traumatic Brain Injury (TBI) in the Animal Model

Preliminary data from TBI animal models treated with decompressive craniectomy have suggested that decompressive craniectomy could reduce edema formation and prevent secondary expansion of the original contusion when compared to non-operative management. Zweckberger et al. utilized a controlled cortical impact model of TBI in a cohort of mice to study the influence of decompressive craniectomy on secondary contusion expansion and brain edema formation, and to determine optimal timing of decompressive craniectomy (25). It was determined that in the surgical groups, there was no secondary expansion of the original contusion and there was a 52% reduction of brain edema compared to the non-surgical group. These benefits were seen with decompressive craniectomy when performed up to 3 h after the initial trauma. Tomura et al utilized a fluid percussion injury model of TBI in a cohort of rats to investigate the influence of decompressive craniectomy on post traumatic brain edema formation. It was found that the non-surgical group demonstrated less cortical water content and greater AQP4 expression when compared to the decompressive craniectomy group.

Decompressive Craniectomy More Than 24 h After TBI

Although there is some controversy regarding the use of decompressive craniectomy in ischemic stroke patients, the use of decompressive craniectomy following human TBI has certainly been more controversial. Three RCTs have analyzed the outcomes of TBI patients after late decompressive craniectomy (more than 24 h from the injury) (see **Table 2**). The DECRA (Decompressive Craniectomy in Diffuse Traumatic Brain Injury) trial published by Cooper et al. in 2011 was a landmark RCT which informed the outcomes of TBI patients with diffuse injuries who were treated with decompressive craniectomy within 72 h of injury (17). In this study, 155 patients with refractory ICPs >20 mmHg for 15 min within a 1-h period were randomized into a decompressive craniectomy group (bifrontal decompressive craniectomy) or a maximal medical management group. On average, the time from injury to surgery was 38.1 h, with a range of 27.1–55.0 h. In this study, Cooper et al. determined that bifrontal decompressive craniectomy decreases ICP and the length of stay in the intensive care unit, but is associated with more unfavorable outcomes. There are, however, some criticisms involving the DECRA trial. First, the randomization was uneven between the 2 groups. There were more patients with non-reactive pupils in the decompressive craniectomy group than the medical therapy group (27 vs. 12%, respectively [$p = 0.04$]). It can be argued that more patients in the decompressive craniectomy group already demonstrated signs of herniation prior to treatment which may obfuscate the therapeutic benefit from a decompressive craniectomy. Indeed, the harm associated with decompression was no longer statistically significant when a statistical control for unreactive pupils was performed. Other issues included the relatively small sample size and that only bifrontal decompressive craniectomy without falx sectioning was allowed. Some researchers believe DECRA was too aggressive and that ICP elevations should have been sustained for longer durations prior to considering surgery. Lastly, there were no standardized rehabilitation protocol for the enrolled patients.

After the DECRA trial, the therapeutic effect of decompressive craniectomy in TBI patients remained unclear, particularly in patients with focal pathology and when a lateral decompression is performed. In 2016, Hutchinson el al. published a multicenter (48 centers, 19 countries) RCT study named RESCUEicp (Trial of Decompressive Craniectomy for Traumatic Intracranial Hypertension) in which a cohort of 408 patients with TBI and refractory elevated ICP (>25 mmHg for at least 1 h) were randomized into a decompressive craniectomy group or a maximal medical therapy group (18). In this pragmatic study, 44% of patients were enrolled after 72 h. RESCUEicp was

TABLE 2 | Decompressive craniectomy for TBI studies.

	Author	Study design	Patients		Treatment	Total no of patients	Time to DC	Mortality *n*(%)	GOS at 6 months	GOS at 12 months	
TBI	Cooper et al. (17)	Randomized controlled trial	Adults with TBI	Age 15–59 years, severe, non-penetrating brain trauma,	DC	73	Performed within 72 h after injury; a large bifrontotemporoparietal craniectomy with bilateral dural opening	14 (19)	Median = 3 (IQR 2–5)	NA	DC decreases ICP and the length of stay in the intensive care unit, but is associated with more unfavorable outcomes.
					Medical management	82	NA	15 (18)	Median = 4 (IQR 3–5)	NA	
	Hutchinson et al. (18)	Randomized controlled trial	Adults with TBI	Age 10–65, abnormal CT scan of the brain, intracranial-pressure monitor already in place, and have raised intracranial pressure (>25 mm Hg for 1–12 h)	DC	202	Performed at any time. 44% were enrolled after 72 h	59 (30.4)	Favorable outcomes (upper severe disability or better): 42.8%	Favorable outcomes (upper severe disability or better): 45.4%	When compared to medical management, DC resulted in lower mortality and higher rates of vegetative state, lower severe disability, and upper severe disability. The rates of moderate disability and good recovery were comparable between both groups.
					Medical management	196	NA	93 (52)	Favorable outcomes (upper severe disability or better): 34.6%	Favorable outcomes (upper severe disability or better): 32.4%	
	Qiu et al. (19)	Randomized controlled trial	Adults with TBI	Patient age 18–65, acute post-traumatic brain swelling on CT with > 5 mm midline shift, contusions <25 ml, compressed basal cisterns, and GCS 8 or less	Unilateral DC	37	DC for all patients within 2 to 24 h after admission	10 (27)	1: 10 (27%); 2: 1 (3%); 3: 5 (14%); 4: 6 (16%); 5: 15 (41%)	4 or 5 (56.8%)	Unilateral DC is superior to control temporoparietal craniectomy in lowering ICPs, reducing the mortality rate, and improving neurological outcomes.
					Control (unilateral routine temporoparietal craniectomy)	37	DC for all patients within 2 to 24 h after admission	21 (57)	1: 21 (57%); 2: 0 (0%); 3: 4 (11%); 4: 7 (19%); 5: 5 (14%)	4 or 5 (32.4%)	

(Continued)

TABLE 2 | Continued

Author	Study design	Patients		Treatment	Total no of patients	Time to DC	Mortality *n*(%)	GOS at 6 months	GOS at 12 months	
Taylor et al. (20)	Randomized controlled trial	Pediatric patients with TBI		DC	13	DC was performed at a median of 19.2 h (range 7.3–29.3 h).	3 (23.1)	Favorable: 7 (53.8%); Unfavorable: 6 (46.2%)	NA	DC may be superior to medical management of in children with TBI in reducing ICP and improving functional outcome and quality of life.
Cianchi et al. (21)	Retrospective cohort	Adults with TBI	186 patients with TBI were retrospectively studied from 2005–2009	Early DC	41	DC was performed within 24 h of TBI	12 (29.3)	Average GOS = 3.3	NA	Hospital mortality rates and Glasgow Outcome Scale at 6 month follow up were comparable between all groups
				Late DC	21	DC was performed after 24 h of TBI	6 (28.6)	Average GOS = 3.0	NA	
				Medical management	124		30 (24.2)	Average GOS = 3.6	NA	
Bagheri et al. (22)	Prospective cohort	Adults with TBI	Severe TBI patients with midline shift > 5 mm and who were candidates for DC according to their initial brain CT scan from 2011–2014.	Early DC	61	DC performed 4.5 ± 2 h after trauma	NA	GOS > 3, 54.1% (33 patients)	NA	Patients whose age was >60 and a GCS <5 did not benefit from early decompressive craniectomy
Jagannathan et al. (23)	Retrospective cohort	Pediatric patients with TBI	23 patients age < 18 who underwent DC for Trauma were analyzed 1995–2006	DC	23	DC performed on avg 68 h (range 24–192)	7 (30.4)	NA	Avg GOS at 2 years = 4.2 (median 5)	Although the mortality rate remains high, DC is effective in reducing ICP and is associated with good outcomes in survivors (81% returning to school)
Shackelford et al. (24)	Retrospective cohort	Adults with TBI	Patients with combat-related brain injury between 2005 and 2015 who underwent DC at deployed surgical facilities	DC	486	Quintile 1: DC 30–152 min after TBI; Quintile 2: DC 154–210 min after TBI; Quintile 3 DC 212–320 min after TBI; Quintile 4: DC 325–639 min after TBI; Quintile 5: DC 665–3,885 min after TBI	Quintile 1: 23; Quintile 2:7%; Quintile 3: 7%; Quintile 4: 19%; Quintile 5: 14%	NA	NA	Mortality was significantly lowered when time to craniectomy occurred within 5.33 h of injury

intended to study a distinct population of patients as compared with DECRA. The DECRA trial looked at decompression within 72 h after diffuse TBI, whereas the RESCUEicp trial analyzed decompressive craniectomy as salvage therapy for refractory intracranial hypertension. Moreover, patients with intracranial hematoma were not included in DECRA trial, but accounted for about 20% of the RESCUEicp trial. Unilateral craniectomy was not permitted in DECRA trial but was allowed in the RESCUEicp trial. At 6 months, the patients in RESCUEicp's decompressive craniectomy group exhibited lower mortality but higher rates of vegetative state, "lower severe" disability, "upper severe" disability, and comparable rates of moderate disability and "good recovery" when compared to the medical management group. It should also be noted that in the subgroup analysis comparing decompressive craniectomy performed before 72 h and at 72 h or more, there were no differences noted in functional outcomes. In interpreting this trial it is important to consider that 37.2% (73 patients) of the patients in the medical group ultimately underwent decompressive craniectomy. Notably, ten patients were excluded from analysis due withdrawal/lack of valid consent. Seven additional patients in the medical group were lost to follow-up. It is particularly important to consider that the majority of the patients in the RESCUEicp trial had diffuse injuries (78.6% of all study patients between the surgical and medical therapy groups) and underwent bifrontal decompressions (81.3% of the surgical group) despite the intent to enroll a distinct population from DECRA. With this in mind, the authors of this manuscript view RESCUEicp as confirming the findings of DECRA without substantially informing the use of decompressive craniectomy in patients with focal pathology, and the role of lateral decompressions.

Due to the paucity of data analyzing the importance of timing of decompressive craniectomy in outcomes of TBI patients, a meta-analysis published by Zhang et al. demonstrated that early decompressive craniectomy within 36 h could result in better prognosis based on the Glasgow Outcome Scale scores at 6 months when compared to patients operated on >36 h from the initial injury (5). The meta-analysis included 10 studies with four randomized controlled trials. On sub-group analysis, Zhang et al. determined that decompressive craniectomy could reduce mortality rate, lower ICPs, decrease ICU stay, but could also increase complication rate.

Decompressive Craniectomy Within 24 h of TBI

While the aforementioned studies analyzed outcomes following decompressive craniectomy performed more than 24 h from time of injury, there have been efforts to analyze outcomes in TBI patients treated with early decompressive craniectomy within 24 h of injury. To that end, Cianchi et al. published their findings from a retrospective analysis which looked at the outcomes of early vs. late decompressive craniectomy compared to maximal medical management in treating TBI patients (21). In this study, 186 TBI patients were divided into early decompressive craniectomy (surgery within 24 h of TBI), late decompressive craniectomy (surgery after 24 h, on average 7.7 days after TBI), and maximal medical management groups. Hospital mortality rates and Glasgow Outcome Scale at 6 month follow up were comparable between all groups; however, the 6 month mortality rate was significantly less for the maximal medical management group compared to the early and late decompressive craniectomy groups (29, 48.8, 42.9%, respectively [$p = 0.02$]) (21). One of the main limitations of this analysis is the retrospective study design. Inherently, patients in the control group had intracranial pressures that were adequately treated with medical therapy whereas patients who received decompressive craniectomy failed medical therapy. It is therefore reasonable to conclude that the patients who underwent decompressive craniectomy had, on average, a more severe TBI. A more appropriate control group would include patients who were non-responders to medical treatment who were not treated with late decompressive craniectomy; however, there are obvious ethical considerations limiting such a study design.

To better address the importance of early decompressive craniectomy in TBI patients, Qiu et al. published an RCT analyzing the outcomes of early decompressive craniectomy in TBI patients (19). Seventy-four patients were randomized to either unilateral decompressive craniectomy or a control group which consisted of a unilateral routine temporoparietal craniectomy. All surgery occurred between 2 and 24 h (average 5.8 h) after admission. Enrolled patients needed to demonstrate >5 mm of midline shift on CT and compression of the basal cisterns. In this RCT, the entire cohort had progressed to some form of radiographic herniation. The mortality rates at 1 month after treatment were 27% in the unilateral decompressive craniectomy group and 57% in the control group. At 1 year follow up, good neurological outcome (GOS Score of 4–5) were 56.8% for the decompressive craniectomy group and 32.4% for the control group ($p = 0.035$). In contrast to the previous stroke studies which demonstrated that decompressive craniectomy after herniation does not confer any functional benefit, Qiu et al. concluded that unilateral decompressive craniectomy after radiographic signs of herniation may be superior to the control group at lowering ICPs, reducing the mortality rate, and improving functional outcome. It should be reiterated that all surgeries were performed within 24 h which is considered to be "early" compared to the timing of decompression reported in most of the TBI in the literature.

Bagheri et al. corroborated the findings of Qiu et al. and published their findings from a prospective study of 61 patients who underwent rapid decompressive craniectomy (within 4.5 ± 2 h) after trauma to assess factors associated with prognosis and outcome (22). Of the 61 patients, 54.1% demonstrated favorable functional outcomes; however, patients with ages older than 60 years, bilateral non-reactive mydriasis, critical head injury (GCS<5), or with >1 cm midline shift had worse outcomes. Bagheri argued that patients whose age was >60 and a GCS <5 did not benefit from early decompressive craniectomy.

Lastly, a large retrospective review involving 486 patients with combat related TBI who underwent decompressive craniectomy demonstrated that decompression within 5.33 h from TBI was associated with improved survival (24). The mortality of the patients were reported by time interval related quintiles: quintile

1 was defined as decompressive craniectomy 30–152 min after TBI, quintile 2 was defined as decompressive craniectomy 154–210 min after TBI, quintile 3 was defined as decompressive craniectomy 212–320 min after TBI, quintile 4 was defined as decompressive craniectomy 325–639 min after TBI, and quintile 5 was defined as decompressive craniectomy 665–3,885 min after TBI. The postoperative mortality was 23, 7, 7, 19, and 14% respectively. Mortality was significantly lowered when time to craniectomy occurred within 5.33 h of injury. While providing some insight into the possible importance of ultra-early decompressive craniectomy on survival, the retrospective design and the lack of long term functional outcome data limits the conclusions that can be drawn from this study.

Although more research is needed, decompressive craniectomy remains a frequently performed treatment—generally of last resort—for many patients with severe TBI. Much additional research is needed to optimize how and when this surgery is performed. In contrast to the findings in the stroke data, preliminary data for TBI studies demonstrate that decompressive craniectomy after acute herniation may still be beneficial in improving mortality and functional outcomes. Although more data are needed, TBI patients treated with early decompressive craniectomy seem to have lower mortality and potentially better functional outcomes than TBI patients treated with late decompressive craniectomy. As with the stroke data, the analysis of outcome for TBI patients in relation to herniation events was insufficiently described in relevant studies, and it is not possible to determine whether early surgery is beneficial due to avoiding herniation or whether there is a benefit to early surgery independent of herniation. While the larger RCTs indicate that decompressive craniectomy may increase the survival rate and concomitantly increase rates of severe disability including vegetative state, subsequent trials with a shorter duration to decompressive craniectomy have demonstrated improved functional outcomes and less mortality.

Early Decompressive Craniectomy in Pediatric TBI Patients

Some published data demonstrate that early decompressive craniectomy may be beneficial in the pediatric population. To that end, Taylor et al. published the only RCT analyzing outcomes of early decompressive craniectomy in the pediatric population (20). Twenty-seven children who had sustained ICP elevation after TBI were randomized to the medical management group or the decompressive craniectomy group. Early bitemporal decompressive craniectomy was performed for the surgical group at a median of 19.2 h (range 7.3–29.3 h) from the time of TBI. Outcome was assessed 6 months after the TBI using a modification of the Glasgow Outcome Score (GOS) and the Health State Utility Index. At 6 months, 54% of children in the decompressive craniectomy group had good outcomes or mild disability at 6 months compared to 14% of children in the control group. Taylor et al. concluded that in pediatric TBI patients with refractory ICPs, patients treated with early decompressive craniectomy are more likely to have reduced ICPs and improved functional outcome than children treated with maximal medical therapy alone. While this is the only RCT published regarding decompressive craniectomy in the pediatric population, this study has received some criticism because it involved an unusual decompressive surgery in which the dura was not opened, and because it accrued a small number of patients over a long study period.

Jagannathan et al. corroborated the findings from Taylor et al. in their retrospective review on the outcomes of 23 pediatric patients who underwent decompressive craniectomy for TBI (23). The time to decompressive craniectomy was on average 68 h (range 24–192). Despite having longer time to decompressive craniectomy compared to Taylor et al., the mean GOS score at the 2-year follow-up examination was 4.2 (median 5). At latest follow up, 81% of the patients returned to school, and only 18% were dependent on caregivers. It should be noted that the outcomes in the Taylor et al. cohort were analyzed at 6 months, whereas the outcomes in the manuscript by Jagannathan et al. were analyzed at 2 year follow up, substantially confounding a comparison of the two trials. Although more data are needed, it is possible that earlier decompression may not be as important in improving long term outcomes in the pediatric population as has been shown in the adult population.

With the limited data at hand, it appears that the pediatric population has better functional outcomes with decompressive craniectomy regardless of timing when compared to medical management. Unfortunately, direct comparisons between early and late decompressive craniectomy have not been made in the pediatric population. Larger RCTs with direct comparisons will be needed to determine if timing plays a role improving outcomes in the pediatric population.

Future Directions: Decompressive Craniectomy Based on Biologic and Radiographic Metrics

While there are data validating the benefits of early craniectomy based on specific time windows and clinical correlates of herniation, there are growing data that there may be other biologic and radiographic metrics to help guide timing of decompressive craniectomy for TBI and stroke. Strict control of intracranial pressures and cerebral perfusion pressures alone does not necessarily prevent cerebral hypoxia (26). Recent data have demonstrated that measurement of brain tissue oxygen tension ($P_{bt}O_2$) may more precisely measure the adequacy of cerebral perfusion, and could be a useful adjunct for deciding on the timing of decompressive craniectomy (27). A $P_{bt}O_2$ below 20 mmHg has been associated with poor outcomes in TBI patients (28). Reithmeier et al. published data on the effects of decompressive craniectomy on ICPs and $P_{bt}O_2$ based on the continuous monitoring of 15 patients and determined that $P_{bt}O_2$ monitoring could serve as a useful tool for timing craniectomy (2). One criticism of $P_{bt}O_2$ is that its measurements are based on data from the confines of a small volume of brain tissue which may not adequately reflect the oxygenation of a larger expanse of compromised brain. Other potentially useful biologic metrics include the pressure reactivity index (PRx) which is the correlation coefficient between mean intracranial pressure

(ICP) and mean arterial blood pressure. This could be used as a surrogate marker of cerebrovascular impairment (29). There have also been preliminary data suggesting that surrogates for blood-brain-barrier disruption, defined by a ratio of total CSF protein concentrations to total plasma protein concentration, may also be useful for prognosis and treatment (30). Advances in imaging modalities may also be utilized to guide the treatment trajectory. The infarct growth rate (IGR) between two CT scans may also be a useful tool for timing craniectomy. Kamran et al. published a retrospective, multicenter cross-sectional study of 182 patients to identify factors for selecting the timing of craniectomy (31). The IGR on the second CT was one of the five factors identified as having the strongest association with craniectomy. Patients who survived without surgery had the slowest IGRs. On another retrospective cohort of 137 patients, Kamran et al. demonstrated that IGR was identified as an independent predictor of early surgery (32). The second infarct growth rate [IGR2] >7.5 ml/hr was associated with surgery under 48 h. Both first infarct growth rate [IGR1] and second infarct growth rate [IGR2] were nearly double in patients with early surgery within 48 h. Although more data are needed, monitoring the infarct growth rate could help determine when a neurosurgeon should pursue decompression. While promising, these biologic and radiographic metrics still require more data before they are used to counsel patients regarding treatment course and prognosis.

CONCLUSION

Although there is much controversy surrounding optimal timing of decompressive craniectomy in patients with stroke and TBI, data have suggested that early decompression within 24 h has a tendency to improve mortality and functional outcomes for both conditions when compared to decompression performed after 24 h. In stroke patients, decompression before clinical signs of herniation yields improved functional outcomes when compared to decompression after clinical signs of herniation. Surgery after clinical deterioration may be too late to impart any functional benefit in stroke patients. In contrast to the stroke data, preliminary TBI data have demonstrated that decompressive craniectomy after signs of herniation may still lead to improved functional outcomes compared to medical management. In adult TBI patients, early decompressive craniectomy within 24 h may improve mortality and functional outcomes when compared to decompressive craniectomy performed >24 h. In fact, data from RCTs suggest that late decompressive craniectomy for TBI may result in worse functional outcomes than maximal medical therapy. In pediatric TBI patients, patients also had better functional outcomes when treated with decompressive craniectomy regardless of timing. High quality studies better informing the timing and indications for decompressive craniectomy are needed for both ischemic stroke and TBI. The additional data provided by imaging and advanced neuromonitoring could also be useful adjuncts in guiding decision making.

AUTHOR CONTRIBUTIONS

AS: Conceptualization of the manuscript, literature review, data analysis, and manuscript writing. SA: Data analysis and revision consultant. GH: Supervised, edited/wrote the manuscript and literature/data analysis.

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The Role of Decompressive Craniectomy in Limited Resource Environments

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Decompressive craniectomy (DC) is a neurosurgical procedure useful to prevent and manage the impact of high intracranial pressure (ICP) that leads to brain herniation and brain's tissue ischemia. In well-resourced environment this procedure has been proposed as a last tier therapy when ICP is not controlled by medical therapies in the management of different neurosurgical emergencies like traumatic brain injury (TBI), stroke, infectious diseases, hydrocephalus, tumors, etc. The purpose of this narrative review is to discuss the role of DC in areas of low neurosurgical and neurocritical care resources. We performed a literature review with a specific search strategy in web repositories and some local and regional journals from Low and Middle-Income Countries (LMICs). The most common publications include case reports, case series and observational studies describing the benefits of the procedure on different pathologies but with several types of biases due to the absence of robust studies or clinical registries analysis in these kinds of environments.

Keywords: decompressive craniectomy, low- and middle-income countries, brain injury, neurological emergencies, low resources areas

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INTRODUCTION

Decompressive craniectomy (DC) is a neurosurgical procedure where some part of the skull bone is removed for prevent pathological rise in intracranial pressure (ICP), brain herniation and brain tissue ischemia. The procedure improves cerebral hemodynamics and brain oxygenation in patients with high ICP, which could decrease mortality and disability in some cases (1). Several intracranial conditions can generate high ICP, and timely treatment of these emergencies is essential to ameliorate intracranial hypertension that generates hypoxia, ischemia and cerebral herniation (2, 3). In low- and middle-income countries (LMICs) neurosurgical emergency care is sometimes delayed due to the lack of neurosurgical work-force or the absence of formal prehospital systems (4–6). Additionally, an absence of post-operative care infrastructure like intensive care units (ICUs) can generate difficulties in the application of protocols of care, designed in high-income settings (7). As an example, in severe TBI cases secondary to road accidents, the transfer of patients to hospitals with neurosurgical capability can take longer times, delaying specialized management or treatment, creating a natural "selection" process, where more sick patients will die and less severe patients will deteriorate over the next hours (8, 9). Facing this reality, early primary DC has been proposed as a common strategy for bring some "hope" of improvement in patients that arrive in a considerable window of treatment (regularly first 24 h) but will

not receive immediately ICU care in the following days after the surgery, because lack of availability. In this opinion article, we will analyze published studies describing the use of DC in the management of neurosurgical emergencies in the context of LMICs.

MATERIALS AND METHODS

We performed a wide-range search using specific search terms in PubMed filtering for human studies, 2001 to 2018, case reports, observational studies, clinical reports, clinical studies, guidelines, systematic reviews, randomized control trials, and multi-center studies to identify articles assessing the use of DC for neurotrauma and brain injury in LMICs. Search strategy is available as **Supplementary Material**. We also performed free-text searches for key words like "decompressive craniotomy" or "low- and middle-income countries" in Google Scholar, DIMDI and some regional journals from Africa, Asia, Latin America, Eastern Europe and South Pacific Region. Filters included English, Portuguese, Spanish and French, from 2001 to 2017. Finally, we reviewed the references of articles identified through this search strategy to identify additional citations for review. We included in this narrative review all human studies assessing the use of DC for neurotrauma or acute brain injury, including stroke, thrombosis, tumor, or infection, in both adult and pediatric patients. For our purposes, decompressive craniectomy encompassed unilateral, bilateral and hemi-craniectomy. We excluded non-human research and articles assessing the use of DC in countries that do not meet World Bank criteria for LMICs, with the exception of Argentina, a high-income country (HIC), as studies from this country contributed to an understanding of regional uses of DC in LMIC regions like Latin America.

RESULTS

Our search identified more than 2000 citations, including 1,148 studies citations from PubMed. After removing duplicate articles, non-human research, and studies not related to DC or LMICs, we included forty-five studies evaluating the role of DC in neurotrauma and forty-eight additional articles related to the use of the DC in non-traumatic neurosurgical emergencies (articles are described in the **Supplementary Material**). Of these studies we review only the ones with clear description of methodology, outcome descriptions using validated scales and studies describing the surgical technique.

Studies From LMICs Related to TBI

We found eight studies from the regions of Latin America, Caribbean and North America discussing the role of DC in TBI. Most of the studies were retrospective, and assessed outcomes such as mortality, survival, and Glasgow Outcome Scale (GOS) or modified Rankin Scale (mRS). Five studies were found from Sub-Saharan Africa, including two from Nigeria, two from South Africa and one from Cameroon. Twelve studies were identified from the East Asia Pacific region. In the Europe & Central Asia region we found three studies from Turkey. From the Middle East, North Africa and South Asian region, we identified 12 studies: three from Pakistan, three from India, three from Afghanistan and Iraq (wartime) and three additional studies from Iran, Jordan and Afghanistan (**Supplementary Table 1**).

The biggest study from Argentina (10) includes a description of 206 pediatric and adult TBI patients managed with or without DC. Mortality was higher in the patients without DC. A study from Colombia (11), evaluated 106 patients under early hemispheric DC with 66% with GOS 4–5 (moderate deficit and normal neurological status) as outcome after 12 months. Three studies of patients with gunshot wounds to the head, from Mexico, Argentina and Colombia (12–14) evaluated DC as therapeutic options with good survivals between 34 and 74%. The first two studies did not specify the DC technique, but the other used hemispheric and bihemispheric techniques for DC. Studies from Cuba (15, 16) analyzed pediatric patients with bi-frontal and unilateral DC. Nearly 60% of the patients in both studies survived with GOS 4-5.

Observational studies from Sub-Saharan Africa, including samples from Nigeria, South Africa & Cameroon, also reported low mortality rates in patients under hemispheric DC (17–19) or hemispheric and bi-frontal DC (20–22).

Studies from China (23–26) show different results with lower mortality in patients under DC with mixed techniques (unilateral and bi-frontal) in pediatric and adult population. In general survival with GOS 4-5 was over 50%. Other Chinese studies (27, 28) compare early vs. late interventions and small to larger decompressions, finding better outcomes in early and large decompressions.

Studies from Mongolia (29), Malaysia (30), and Thailand (31) also were consistent with benefits of unilateral or bilateral decompressions.

In the Middle East, North Africa and South East Asia regions, several observational studies have been performed in civilian and war settings. A study from Iran (32) with 142 patients and another from India (33) with 1,236 patients treated with unilateral and bilateral decompressions have the largest samples of civilian settings with favorable outcomes in both studies. In the second one, 49% of patients survived with GOS 4-5 at discharge. In Afghanistan and Iraq, studies by military neurosurgeons (34–36), showed the same trend of over 50% survival. In Pakistan and India, other studies have been performed including samples of pediatric and adult patients (37–39). These studies also show survivors with favorable outcome in more than 50% of the patients, using different techniques.

Studies From LMICs Related to Stroke and Cerebral Venous Sinus Thrombosis (CVST)

We found three studies from Latin American, Caribbean and North American regions (two from Brazil and one from Colombia). Nine studies were identified from the East Asia Pacific region (eight from China and one from Malaysia). Two were found from Europe and Central Asia region (Turkey). Twelve studies were found from Middle East, North Africa and South Asia region: among these, six were from India, two from

Iran and one each from Egypt and Pakistan. Among all these studies, patients underwent hemicraniectomy and this operation improved survival as compared to conservative medical therapy. Among survivors, those who underwent surgery had better outcomes and improved quality of life, measured with the modified Rankin Scale (mRS). The DC also was used in studies of CVST: 1 study was found from East Asia Pacific (China), and 5 from Middle East, North Africa and South Asia (four from India and one from Pakistan). All studies showed improved survival rate and favorable outcomes in patients who underwent DC (see **Supplementary Tables 1–3**).

A study from Brazil (40) presented a cohort of 60 patients with malignant middle cerebral artery (MCA) infarction who underwent unilateral DC. They showed that mortality was higher (67%) in patients > 60 years, while only 44% of the patients from the younger group (<60 years) had mRS 5–6 at 90 days follow-up. A study from China (41) presented data of 219 adult patients in which 31 patients underwent unilateral DC after malignant MCA infarct; they showed higher favorable outcome (32.2%) in patients who underwent DC vs. those who only had medical management (13.3%) at 1-year follow-up. An Indian study (42) showed absolute risk reduction of 45% in mortality at 1-year in the patients who underwent DC vs. medical treatment only in malignant MCA infarct. They found that surgery reduced the odds of moderate to severe disability (mRS 4) by 93.5%. Similarly, another study from India (43) showed 73% survival at 1-year post-surgery, and among the survivors 72% attained the ability to walk independently at this post-surgical milestone. A third study from India (44) presented data of 53 patients; 60% among these were older than 60 years. Their study found that 78% patients aged below 60 years had mRS 0-3 (good outcome) at discharge while only 38% patients aged above 60 years had similar outcome, mRS 0-3, at discharge, demonstrating that DC reduces morbidity and mortality in patients below 60 years. A Malaysian study (45) presented data of 125 patients and among those 90 had DC and 35 received medical treatment. They showed that DC resulted in reduced mortality (30.0 vs. 54.3%) and favorable GOS at discharge. A study from Iran (46) with 60 participants reported reduced mortality and better average GOS (2.93 vs. 1.53) in surgical group vs. medical treatment group. Similarly, they observed better mRS in surgical vs. medical management (3.27 vs. 5.27).

A study from Pakistan (47) showed that DC is beneficial in both dominant and non-dominant side infarctions. In this study the mean surgery time from diagnosis was 60.61 h, which is beyond the recommended period (within 24–48 h). Another study from Iran (48) presented 30 patients with large and deep seated supratentorial intracerebral hemorrhage (ICH) that were randomly divided either in a group where they only received large decompressive hemicraniectomy or in a group where they underwent craniotomy with clot evacuation. They showed that there was no difference in mortality and GOS at 6-months but good outcome (GOS 4-5) was higher (35.3%) in patients who had undergone hematoma evacuation vs. those who had large DC only (30.7%).

A study from Brazil (49) investigated the role of DC in patients with intracranial aneurysms. In their study, they presented 37 cases of DC performed in patients with aneurysms and among them 22 had ruptured aneurysms. In their cohort, 60% survived after DC and they recommended early surgery because it reduced mortality and morbidity.

Six studies from LMICs were found about the role of DC in the management of CVST. A retrospective study with 58 adults from China (50) showed favorable outcomes in 56.9% of the patients who underwent hemicraniectomy for CVST. Similarly, another observational retrospective study from India (51) with 34 adult patients also presented favorable outcomes in 76.4% of patients who underwent unilateral DC for CVST management.

STUDIES OF DC IN OTHER PATHOLOGIES

The procedure also has been applied in management of conditions like infections and tumors; we found 3 case reports regarding the role of DC in infections from Latin American, Caribbean and North American Regions (1 each from Argentina, Brazil and Peru). Two case reports about infection were found from Middle East, North Africa and South Asia region (India). A few other case reports were found regarding the use of DC in malignancies, intracranial demyelinating lesions and vasospasm after subarachnoid hemorrhage (**Supplementary Material**).

Two case reports from India (52, 53) showed favorable outcomes in patients who underwent hemicraniectomy for the management of Herpes Simplex Encephalitis and Cerebral Toxoplasmosis, respectively. Case reports from Argentina and Mexico (54, 55) showed use of DC in the management of tumors and patients initially improved post-operatively but complications including death and metastasis were observed in long-term follow-up. Another case report of 2 pediatric patients with ICH in acute leukemia from India (56) showed favorable outcomes following DC.

DISCUSSION

This literature search identified several studies demonstrating the use of decompressive craniectomy in LMICs, for conditions such as traumatic brain injury, stroke, CVST, and other neurosurgical emergencies. Publications assessing the use of decompressive craniectomy for traumatic brain injury in LMICs showed overall favorable outcomes, assessed either as overall survival or GOS on discharge. However, these studies were largely limited to case reports, case series and observational studies from single centers describing the benefits of the procedure on different pathologies. While several studies demonstrated lower mortality or higher GOS in those patients undergoing decompressive craniectomy, these studies were limited by the absence of robust studies or clinical registries analysis in these kinds of environments. In addition, there is substantial variability among the studies with regard to timing and type of decompressive craniectomy performed, as well as in study population (adult or pediatric). While these limitations make it difficult to compare

results between studies, it can be seen that decompressive craniectomy is a commonly used procedure for the management of TBI, stroke, and other neurosurgical emergencies in LMICs, and that this procedure has benefits for survival in certain settings.

Recent developments coming specifically from LMICs in the aspects of DC have been described within the brief discussion of the articles included. Due to significant variability in the conditions, procedures, and outcomes assessed we were unable to perform a full systematic review of this topic. However, we conducted a comprehensive search of the literature that identified relevant articles from these environments from many regions of the world.

CONCLUSIONS

Decompressive craniectomy is a frequently used procedure for the management of neurosurgical emergencies in LMIC's according to the available medical literature. The most common publications include case reports, case series and observational studies describing the benefits of the procedure on different pathologies. In most of the observational studies there is a common trend of benefit from the procedure, but the low methodological quality of these studies and a high risk of publication bias does not allow any type of conclusions valid for transferability of knowledge in other regions of the world.

AUTHOR CONTRIBUTIONS

AC, AK, JM, JHM, AA, EJ, and AR, contributed equally to the conception, writing and preparation of the manuscript.

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SUPPLEMENTARY MATERIAL

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Decompressive Craniectomy for Traumatic Brain Injury: Postoperative TCD Cerebral Hemodynamic Evaluation

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Background: There are no studies describing the cerebral hemodynamic patterns that can occur in traumatic brain injury (TBI) patients following decompressive craniectomy (DC). Such data have potentially clinical importance for guiding the treatment. The objective of this study was to investigate the postoperative cerebral hemodynamic patterns, using transcranial Doppler (TCD) ultrasonography, in patients who underwent DC. The relationship between the cerebral circulatory patterns and the patients' outcome was also analyzed.

Methods: Nineteen TBI patients with uncontrolled brain swelling were prospectively studied. Cerebral blood circulation was evaluated by TCD ultrasonography. Patients and their cerebral hemispheres were categorized based on TCD-hemodynamic patterns. The data were correlated with neurological status, midline shift on CT scan, and Glasgow outcome scale scores at 6 months after injury.

Results: Different cerebral hemodynamic patterns were observed. One patient (5.3%) presented with cerebral oligoemia, 4 patients (21%) with cerebral hyperemia, and 3 patients (15.8%) with cerebral vasospasm. One patient (5.3%) had hyperemia in one cerebral hemisphere and vasospasm in the other hemisphere. Ten patients (52.6%) had nonspecific circulatory pattern. Abnormal TCD-circulatory patterns were found in 9 patients (47.4%). There was no association between TCD-cerebral hemodynamic findings and outcome.

Conclusion: There is a wide heterogeneity of postoperative cerebral hemodynamic findings among TBI patients who underwent DC, including hemodynamic heterogeneity between their cerebral hemispheres. DC was proved to be effective for the treatment of cerebral oligoemia. Our data support the concept of heterogeneous nature of the pathophysiology of the TBI and suggest that DC as the sole treatment modality is insufficient.

Keywords: decompressive craniectomy, traumatic brain injury, transcranial Doppler ultrasonography, intracranial pressure (ICP), cerebral hemodynamics

INTRODUCTION

Decompressive craniectomy (DC) may effectively decrease intracranial pressure (ICP) and increase cerebral perfusion pressure (CPP) in traumatic brain injury (TBI) patients with refractory elevated ICP (1, 2). However, randomized controlled trials failed to disclose the efficacy of this procedure for improving these patients' neurological outcome (3, 4). This means that ICP control to ensure CPP, as the sole treatment strategy, is not sufficient to achieve satisfactory therapeutic results in most cases. New research should focus on different pathophysiological mechanisms of posttraumatic brain swelling.

Transcranial Doppler (TCD) ultrasonography is a non-invasive and bedside method for real-time assessment of cerebral blood circulation. This technique is routinely used in clinical and scientific scenario (5–8).

To date, few studies have addressed the cerebral hemodynamic and metabolic effects of DC for uncontrolled elevation of ICP (2, 9–15). To our knowledge, there are no studies describing the different cerebral hemodynamic patterns that can occur in TBI patients following DC. Such data potentially have clinical importance, which justifies a study.

The aim of this study was to investigate the postoperative cerebral hemodynamic patterns, using TCD ultrasonography, in patients who underwent DC for uncontrolled intracranial hypertension and brain herniation syndrome. The relationship between the cerebral circulatory patterns and the patients' outcome was also evaluated.

MATERIALS AND METHODS

Study Design and Patient Enrollment

A prospective study on the effects of DC on cerebral hemodynamics for traumatic brain injury (TBI) was conducted from January 1999 to September 2002, at the Hospital das Clinicas of the University of Sao Paulo Medical School. The enrollment criteria were TBI patients presenting with severe brain swelling for whom DC was indicated and in whom preoperative and postoperative TCD ultrasonography had been carried out. Exclusion criteria included penetrating TBI, Glasgow Coma Scale (GCS) score of 3 associated with bilaterally fixed and dilated pupils, and the lack of TCD ultrasonography evaluations. Multisystem trauma patients were not excluded. Participants were characterized in terms of demographic, clinical, and radiological variables. This study was approved by our research ethics committee (CAPPesq).

Patient Population

Nineteen patients met the inclusion criteria for this study. Their ages ranged from 17 to 63 years, with a mean age of 33 ± 14 years. There were 13 male and 6 female patients. Median admission GCS scores was 7, varying from 4 to 13. These patients were divided into two groups. The first group consisted of 9 patients with no focal lesions, in whom severe brain swelling and refractory signs of brain herniation led to DC. The second group was composed of 10 patients who presented with an expanding hematoma (contusion hemorrhage, extradural and/or subdural hematoma), which had been initially removed, and developed afterwards severe brain swelling. Twenty percent of patients had a hypotensive insult at hospital admission. Demographic, clinical, and imaging data for each patient were presented in our previous studies (10, 16).

General Management Protocol

Guidelines of the American College of Surgeons (Advanced Trauma Life Support) and of the American Association of Neurological Surgeons were adopted for the clinical e surgical management of the patients (10). All patients with neurological deterioration underwent brain computerized tomography (CT) scans. ICP monitoring was not part of the study.

Indications for Surgical Decompression

DC was performed in patients with neurological deterioration and CT scans disclosing predominantly unilateral diffuse brain swelling associated with mass effect, a midline shift and/or obliteration of peri-mesencephalic cisterns. Neurological worsening was defined as a decrease in GCS score and/or unilaterally or bilaterally unresponsive and dilated pupils. Patients with persisting GCS score of 3 and/or bilaterally fixed and dilated pupils were not operated on. The surgical technique consisted of large hemicraniectomy with dural opening over the most swollen cerebral hemisphere.

Evaluation of Cerebral Hemodynamics

TCD examinations were performed before surgery while the patient waited to go to the operating room, or while the surgical team prepared the patients in the operating room. Postoperative TCD examinations were obtained soon after the completion of incision closure and dressing, while the anesthesiologist prepared the patient in the operating room. Portable 2 MHz pulsed TCD equipment (Pioneer TC 2020 EME; Nicolet Biomedical, Madison, WI) was used to measure the blood velocities in the middle cerebral arteries (MCA) and the distal segment of the extracranial internal carotid arteries (ICA), respectively, via temporal and submandibular regions. TCD examinations were performed by an experienced sonographer (EBSS) using a hand-held technique. Monitoring of cerebral blood flow velocities for long periods of time was not performed. The TCD variables were the mean velocity (the time mean of the peak velocities over the course of four cardiac cycles) and the pulsatility index (PI = [systolic velocity–diastolic velocity]/mean velocity).

Systemic arterial blood pressure, body temperature, hematocrit, arterial blood carbon dioxide, and oxygen pressures were noted in each TCD examination.

Definition of TCD Cerebral Circulatory Patterns

High MCA mean blood velocities can occur in both cerebral vasospasm and hyperemia. The Lindegaard ratio (LR), defined as the ratio of MCA mean blood velocity to the ipsilateral extracranial ICA mean blood velocity, can be used to discriminate cerebral vasospasm from hyperemia (17–19). For the calculation of the LR, MCA flow velocities were divided

by the ipsilateral extracranial ICA flow velocities. LR can improve the diagnostic accuracy of TCD in detecting cerebral vasospasm.

MCA mean blood velocities >100 cm/s along with LR <3 were considered as cerebral hyperemia, whereas MCA mean blood velocities <40 cm/s were defined as cerebral oligoemia. MCA mean blood velocities between 40 and 100 cm/s associated with LR <3 were considered as non-specific hemodynamic pattern. MCA mean blood velocities >100 cm/s in conjunction with LR >3 were considered as cerebral vasospasm (17–19).

Categorization of Patients by Cerebral Circulatory Patterns

Participants with hyperemia in both cerebral hemispheres, or hyperemia in one cerebral hemisphere and non-specific hemodynamic pattern in the contralateral hemisphere were defined as having cerebral hyperemia. In contrast, participants with oligoemia in both cerebral hemispheres, or oligoemia in one cerebral hemisphere and non-specific hemodynamic pattern in another hemisphere were considered as presenting cerebral oligoemia. Patients with hyperemia in one cerebral hemisphere and oligoemia in the contralateral hemisphere, as well as patients with cerebral vasospasm, were grouped separately.

Data Collection

Clinical data such as age, gender, accident date, time intervals from accident to hospital admission, and from admission to decompressive craniectomy, brain injury mechanisms, neurological examination (GCS score and pupil activity) at admission, prior to, and following brain decompression, midline brain structures shift, associated intracranial posttraumatic lesions, length of hospital stay, and outcome were extracted from our database.

Clinical Outcome

Glasgow Outcome Scale (GOS) score was determined for all patients approximately 6 months post-injury. Patients were assigned to one of the five categories: death, persistent vegetative state, severe disability, moderate disability, or good recovery. Patients with good recovery (GOS score of 5) or with moderate disability (GOS score of 4) were defined as presenting favorable outcome. Patients who were assigned to the severe disability (GOS score of 3) or to the persistent vegetative state (GOS score of 2) or those who died (GOS score of 1) were considered to have an unfavorable outcome.

Statistical Analysis

Results were expressed as means ± standard deviations. The paired Student's *t*-test, Mann-Whitney *U*-test, the Wilcoxon rank-sum test, and the Fischer exact test were carried out. Spearman correlation coefficients were considered when appropriate. For all statistical tests, a difference was defined as significant when the probability value was <0.05.

RESULTS

Cerebral Blood Flow Velocity Measurements and PI

Preoperative MCA mean blood velocity varied from 8 to 143 cm/s. The average mean blood flow velocities in the MCA were 53 ± 38 and 51 ± 26 cm/s, respectively, in the most swollen cerebral hemisphere and in the opposite side ($p = 0.88$). The PI in the MCA ranged from 0.61 to 7.09. The average PI in the MCA was 1.85 ± 1.56 in the most swollen cerebral hemisphere and 1.73 ± 1.36 in the opposite hemisphere.

Postoperative MCA mean blood velocities varied widely from 39 to 155 cm/s. The average mean blood velocities in the MCA were 94 ± and 76 ± 16 cm/s, respectively, in the decompressed cerebral hemisphere and in the opposite side ($p < 0.05$). The PI in the MCA ranged from 0.46 to 1.30; the average PI in the MCA was 0.81 ± 0.18 in the decompressed cerebral hemisphere and 0.86 ± 0.22 in the contralateral hemisphere.

Following DC, mean blood velocities increased, on average, from 53 ± 38 to 94 ± 33 cm/s in the MCA of the decompressed cerebral hemisphere ($p < 0.01$), and from 51 ± 26 to 76 ± 16 cm/s on the contralateral side ($p < 0.01$), whereas PI decreased, on average, from 1.85 ± 1.56 to 0.81 ± 0.18 in the MCA of the decompressed cerebral hemisphere ($p < 0.01$), and from 1.73 ± 1.36 to 0.86 ± 0.22 on the contralateral side ($p < 0.01$) (**Table 1**).

Classification of Patients and the Cerebral Hemispheres by Hemodynamic Patterns

Prior to DC, 10 patients (52.7%) presented cerebral oligoemia, 3 patients (15.8%) fulfilled the criteria for cerebral hyperemia, and 6 patients (31.5%) were assigned to have non-specific circulatory pattern (**Table 2**). Abnormal circulatory patterns were found in 13 patients (68.5%).

Considering only the most swollen cerebral hemisphere, 10 patients (52.6%) had cerebral oligoemia, 7 patients (36.9%)

TABLE 1 | Cerebral blood flow velocity and pulsatility index before and after decompressive craniectomy.

Variable	Side	Preop	Postop	*P*-value
Flow velocity	Decompressed	53 ± 38 cm/s	94 ± 33 cm/s	$p < 0.01$
Flow velocity	Opposite	51 ± 26 cm/s	76 ± 16 cm/s	$p < 0.01$
Pulsatility index	Decompressed	1.85 ± 1.56	0.81 ± 0.18	$p < 0.01$
Pulsatility index	Opposite	1.73 ± 1.36	0.86 ± 0.22	$p < 0.01$

TABLE 2 | Number of patients according to cerebral circulatory patterns before and after decompressive craniectomy.

Circulatory patterns	Before craniectomy	After craniectomy
Oligoemia	10 (52.7%)	1 (5.3%)
Hyperemia	3 (15.8%)	4 (21.0%)
Non-specific	6 (31.5%)	10 (52.6%)
Vasospasm	–	3 (15.8%)
Hyperemia / Vasospasm	–	1 (5.3%)
Total	19 (100%)	19 (100%)

presented non-specific hemodynamic pattern, and 2 patients (10.5%) had cerebral hyperemia. In the contralateral side ($N = 17$), 3 patients (17.6%) presented cerebral oligoemia, 13 patients (76.5%) showed non-specific hemodynamic pattern, and 1 patient (5.9%) had cerebral hyperemia (**Table 3**). Abnormal circulatory patterns were more frequent in the most swollen cerebral hemisphere than in the opposite hemisphere (respectively, 63.1 vs. 23.5%).

After DC, 1 patient (5.3%) was found to present cerebral oligoemia, 4 patients (21%) fulfilled the criteria for cerebral hyperemia, and 3 patients (15.8%) were assigned to have cerebral vasospasm. One patient (5.3%) was classified as having hyperemia in one cerebral hemisphere and vasospasm in the contralateral hemisphere. Ten patients (52.6%) showed to have non-specific circulatory pattern (**Table 2**). Abnormal TCD-circulatory patterns were found in 9 patients (47.4%).

In the decompressed cerebral hemisphere, no patient had cerebral oligoemia, 11 patients (58%) presented non-specific hemodynamic pattern, 4 patients (21%) had cerebral hyperemia, and 4 patients (21%) were found to have cerebral vasospasm. In the contralateral side ($N = 17$), 1 patient (5.9%) presented cerebral oligoemia, 15 patients (88.2%) had non-specific hemodynamic pattern, and 1 patient (5.9%) showed to have cerebral hyperemia (**Table 3**). Abnormal circulatory patterns were more frequently encountered in the most swollen cerebral hemisphere than in the opposite hemisphere (42 vs. 11.8%, respectively).

Clinical and Cerebral Hemodynamic Variables and Neurological Outcome

There was an inverse correlation between midline brain structures shift and GOS scores at 6 months post-injury ($r = -0.46$, $p < 0.05$). Also, the time interval from hospital admission to DC was inversely correlated with the degree of cerebral blood flow (CBF) velocity increase after surgical decompression ($r = -0.50$, $p < 0.05$) (**Table 4**). There was no correlation between postoperative cerebral circulatory responses and other clinical and imaging variables such as preoperative GCS score, GOS scores at 6 months post-injury, and neurological recovery based on favorable (good recovery and moderate disability) and unfavorable outcome (severe disability, vegetative state, or death) at 6 months follow-up.

DISCUSSION

Role of Surgical Decompression

DC was proved to be effective for the treatment of cerebral oligoemia. Prior to surgery, more than a half of our patients (52.7%) had hemodynamic pattern of cerebral oligoemia (16) while only 5% of them (5.3%) after surgery. This finding can be explained by the decompressive effects of this surgery, which consist of reduction of ICP and increase of CPP, CBF, cerebral microvascular perfusion, and brain tissue oxygenation (1, 2, 12–15, 20). It is important to emphasize that these effects does not necessarily lead to cerebral hemodynamic improvement. In our cases, despite all these decompressive

TABLE 3 | Circulatory patterns in the most swollen cerebral hemisphere and in the opposite hemisphere before and after decompressive craniectomy.

	Before surgery		After surgery	
Circulatory patterns	**Most swollen hemisphere**	**Contralateral cerebral hemisphere**	**Decompressed cerebral hemisphere**	**Contralateral cerebral hemisphere**
Oligoemia	10 (52.6%)	3 (17.6%)	0	1 (5.9%)
Hyperemia	2 (10.5%)	1 (5.9%)	4 (21%)	1 (5.9%)
Non-specific	7 (36.9%)	13 (76.5%)	11 (58%)	15 (88.2%)
Vasospasm	0	0	4 (21%)	0
Total	19 patients (100%)	17 patients (100%)	19 patients (100%)	17 patients (100%)

TABLE 4 | Correlation between neurological outcome and clinical variables and between postoperative cerebral hemodynamic changes and clinical variables*.

	6-Months GOS		CBFV increase decompressed side		CBFV increase opposite side	
	***P*-value**	**Correlation**	***P*-value**	**Correlation**	***P*-value**	**Correlation**
Age	0.319	−0.242	0.29	−0.256	0.556	−0.154
Sex	0.574	0.138	0.801	−0.062	0.802	−0.066
Interval Ad—DC	0.129	0.598	0.028	−0.503	0.03	−0.527
Preoperative GCS	0.113	0.375	0.301	0.251	0.472	0.187
Midline shift	0.044	−0.466	0.651	−0.111	0.27	0.284
CBFV increase decompressed side	0.113	0.645				
CBFV increase opposite side	0.158	0.545				

**Interval Ad—DC, interval between hospital admission and decompressive craniectomy; GCS, Glasgow coma scale; CBFV, cerebral blood flow velocity; GOS, Glasgow outcome scale.*

effects, almost half of the patients (47.4%) still had cerebral hemodynamic disturbances, potentially requiring postoperative cerebral hemodynamic monitoring, and possibly measures of cerebral hemodynamic control.

Clinical Implications

Modern principles on CBF management in TBI patients recommend avoiding states of severe cerebral hyperemia and oligoemia (10, 16, 21). The former may result in cerebral blood volume rise, vasogenic edema enhancement, and the risk of intracerebral hemorrhage, while the latter may lead to cerebral ischemia and infarction. Both hemodynamic states can aggravate cerebral swelling and raised ICP. Therefore, the systemic and cerebral hemodynamic management should aim at adequate CBF, preferably coupled with metabolism, avoiding severe cerebral hyperemia, and oligoemia.

Methodically, causes of cerebral hyperemia (anemia, hypercapnia, arterial hypertension, hypervolemia, increased cardiac output, and cerebral metabolic crisis, drugs that induce microvascular dilation, etc.) must be investigated and treated if indicated. On the other hand, causes of cerebral oligoemia (hypocapnia, arterial hypotension, hypovolemia, dehydration, decreased cardiac output, raised ICP, drugs that induce microvascular constriction, among others) must be considered and corrected if possible. Factors that intensify cerebral metabolic activity (seizures and fever) must be avoided and treated, irrespective of the cerebral hemodynamic status, whether hyperemia or oligoemia, because such factors increase the energy requirement in the brain, worsening the uncoupling between cerebral blood flow and metabolism in cases of cerebral ischemia and/or the uncoupling between cerebral energetic need and brain energy production in cases of non-ischemic metabolic crisis due to mitochondrial dysfunction (22, 23). Cerebral oligoemia detected in our patients was not associated with significant arterial blood hypotension. During TCD examinations, factors that can cause low CBF velocity, such as suboptimal angle of insonation, arterial hypotension, arterial hypocapnia and intracranial hypertension must be considered and ruled out.

Recent papers disclosed that metabolic crisis in TBI patients undergoing DC cannot be explained only by cerebral ischemia (11, 13, 22–24). Some patients showed to have non-ischemic metabolic crisis characterized by impairment of oxidative phosphorylation in mitochondria, leading to failure of brain energy production. Therefore, there are hyperactivity of anaerobic metabolism pathway, failure of brain energy metabolism, and aggravation of cerebral swelling. The brain energetic failure associated with mitochondrial dysfunction triggers the cascade of free radical production, necrosis and apoptosis (11). A higher prevalence of mitochondrial dysfunction and ischemic episodes was reported in unfavorable outcome patients (11), reinforcing the importance of controlling both the cerebral hemodynamics and metabolism.

Non-ischemic metabolic crisis causes cerebral tissue acidosis due to anaerobic metabolism, despite high levels of tissue oxygen; as a consequence, microvascular paresis can occur leading to decrease in cerebrovascular resistance, impairment of cerebral autoregulation and hyperemia (12, 22, 23, 25). A recent review disclosed association between intracranial hypertension and dysfunction of cerebral autoregulation, which can persist after DC (26). The impairment of cerebral autoregulation can reduce the arterial blood pressure threshold needed to maintain suitable CBF (27).

Our results are important for guiding the intensive management of these patients. One patient from our series presented with hemodynamic pattern suggestive of cerebral hyperemia in one hemisphere and vasospasm in the other hemisphere. Therapeutic management of these patients may be challenging, chiefly if both hyperemia and vasospasm are severe. Arterial blood pressure augmentation therapy or surgical decompression for treating cerebral oligoemia may not be suitable for the hyperemic hemisphere; in contrast, measures for decreasing cardiac output may worsen ischemia in the oligoemic cerebral hemisphere. Such patients should be monitored closely with multimodal fashion to achieve a middle ground whereby correction of cerebral hypoperfusion does not cause significant worsening of contralateral cerebral hyperemia (28). It is worth stressing that traumatic intracranial expanding lesions and/or disturbed cerebrospinal fluid circulation contribute to the formation of pressure gradients in the intracranial space (29, 30), such as interhemispheric supratentorial pressure gradients (31), as well as to the hemispheric asymmetry of the pressure autoregulation (32) and critical closing pressure (33). Along with cerebral vasospasm, these pathophysiological events can explain, in part, our findings of cerebral hemodynamic heterogeneity, including heterogeneity between the cerebral hemispheres.

Cerebral Hemodynamic Changes and Outcome

The data of the present study failed to show correlation between cerebral hemodynamics and clinical outcome. This does not mean that those correlations cannot exist. However, the statistical analysis revealed a significant inverse correlation between midline brain structures shift and GOS at 6 months after injury, suggesting that the greater the midline shift, the worse the clinical outcome. Also, a significant inverse correlation was found between the time interval from hospital admission to DC and cerebral hemodynamic changes after DC, indicating that the longer the time interval, the lower the degree of postoperative CBF velocity increases. Both facts can reinforce the idea that DC should be indicated early or, at least, should not be indicated too late.

Limitations

This study has a number of caveats, mainly related to small sample size, possibility of type II error, and difficulties in obtaining serial TCD examinations and clinical data (from mechanical ventilation, sedation, vasopressors, intracranial pressure, cerebral metabolic, and electrical activity, neurological status, among others). Future studies should devise protocols that can investigate the temporal course of cerebral hemodynamics for each patient, and the impact of TCD results on guiding the treatment. Other limitations include the lack of data about the number of patients and the respective reasons for their

exclusions during the recruitment process and the lack of sample size estimation in the planning of this research; the latter may limit the interpretation of the findings related to the correlation between cerebral hemodynamic patterns and clinical outcome. It should be noted that to date there are no data on this subject in the literature that can be used to calculate the sample size.

Concerning the MCA blood velocity threshold for vasospasm detection, flow velocities >140 cm/s can be more appropriate, however the higher the blood velocity, the lower the TCD sensitivity. Taking this into account, both flow velocities >100 cm/s and LR >3 were adopted in this study. The latter can improve the diagnostic discrimination between cerebral hyperemia and vasospasm.

Although little discussed, the diameter of MCA depends on factors such as blood pressure in the vessel lumen, intracranial pressure, and intrinsic vessel wall properties, among others. This means that the diameter of MCA may change following DC, making the interpretation of TCD results more difficult.

CONCLUSION

DC leads to increase in CBF velocity and decrease in PI, indicating reduction in ICP. Our results showed a marked heterogeneity of postoperative cerebral hemodynamic findings among TBI patients with uncontrolled brain swelling who underwent DC, including hemodynamic heterogeneity between their cerebral hemispheres. DC was proved to be effective for the treatment of cerebral oligoemia. Not surprisingly, previous studies on TBI demonstrated cerebral heterogeneity in terms of circulation, pressure autoregulation, critical closing pressure, oxygenation, and metabolism (2, 16, 34). Our data reinforces the concept of heterogeneous nature of the TBI pathophysiology and suggest that DC as the sole treatment modality is insufficient. The combination of therapies (for instance, surgical decompression associated with the control of both CBF and metabolism) can potentially improve patients' outcomes. For the future, patients should be monitored in terms of ICP, cerebral hemodynamics and metabolism to allow individually planned treatments. In clinical practice, the identification of different cerebral hemodynamic and metabolic patterns and their significances may be useful for determining specific therapeutic strategies. TCD can be more used as a bedside monitoring method due to its low cost, non-invasiveness, wide availability, and relatively short time of examination. Unfortunately, this diagnostic tool depends on the operator skill to obtain and interpret the cerebral hemodynamic data, and does not directly quantify the CBF, but only its velocity. The finding of cerebral hemodynamic heterogeneity in severe TBI requires more TCD studies on this issue to have more practical clinical experience.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of Hospital das Clinicas of the University of Sao Paulo Medical School research ethics committee (CAPPesq) with written informed consent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the CAPP.

AUTHOR CONTRIBUTIONS

EB-S-S contributed conception and design of the study. EB-S-S, Md-L-O, RN, KA, EP, and FP collected the clinical data. EB-S-S wrote the first draft of the manuscript after discussions with Md-L-O, RN, KA, EP, and FP wrote some of the methods part. All authors contributed to manuscript revision, read, and approved the submitted version.

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The History of Decompressive Craniectomy in Traumatic Brain Injury

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Decompressive craniectomy consists of removal of piece of bone of the skull in order to reduce intracranial pressure. It is an age-old procedure, taking ancient roots from the Egyptians and Romans, passing through the experience of Berengario da Carpi, until Theodore Kocher, who was the first to systematically describe this procedure in traumatic brain injury (TBI). In the last century, many neurosurgeons have reported their experience, using different techniques of decompressive craniectomy following head trauma, with conflicting results. It is thanks to the successes and failures reported by these authors that we are now able to better understand the pathophysiology of brain swelling in head trauma and the role of decompressive craniectomy in mitigating intracranial hypertension and its impact on clinical outcome. Following a historical description, we will describe the steps that led to the conception of the recent randomized clinical trials, which have taught us that decompressive craniectomy is still a last-tier measure, and decisions to recommend it should been made not only according to clinical indications but also after consideration of patients' preferences and quality of life expectations.

Keywords: decompressive craniectomy, traumatic brain injury, history of head trauma, intracranial hypertension, brain decompression, hemicraniectomy, bifrontal craniectomy

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INTRODUCTION

Intracranial hypertension is a critical event frequently occurring after traumatic brain injury (TBI) as a delayed secondary pathologic process initiated at the moment of injury. Due to the rigid nature of the skull and the dura, brain edema, expanding hematomas, or blossoming of contusions can rapidly exhaust the compensation mechanisms leading to maintenance of a controlled intracranial pressure (ICP). These events lead to a vicious cycle whereby reduced cerebral perfusion pressure (CPP) causes reduction of cerebral blood flow (CBF) and oxygenation, with worsening of brain edema and, eventually, brain herniation, and death. Following failure of medical management, decompressive craniectomy (DC), a procedure consisting on removal of part of the skull and opening of the underlying dura, can be used as a last-tier therapy to mitigate ICP elevation. During the last century, the popularity of DC has known phases of glory and oblivion, mainly related to alternating surgical outcome, with too many patients suffering severe disability and vegetative state. However, advances in neurointensive care and neuroimaging have led to an increased interest in the use of DC in the 2000s, culminating in the publication of randomized clinical trials (1–3). Despite controversies, the use of DC has been introduced in TBI guidelines, and its efficacy has

been recently considered to be beneficial in terms of improving overall survival as a last-tier therapy, compared to medical treatment (4, 5).

We retrace the historical passages which marked the evolution of DC in TBI.

EARLY HISTORY

Trephination and Inadvertent Skull Decompression

The earliest evidence of skull trephination dates back to 10,000 BC at the beginning of the Neolithic period and has been deduced by studying the major skull collections: the French Prunières collection and the Peruvian skulls (6). There is limited archeological evidence of trephined skulls found in Egypt, except for few cases analyzed by Pahl in the book Altägyptische Schädelchirurgie (7).

Later, the practice was well-described in the Greek Era by Hippocrates (8). In Alexandrian school, the main records in head injured patients come from the scientist Aulus Aurelius Cornelius Celsus (25 BC–AD 50). He advocated trephination when patients developed symptoms after trauma despite the absence of any fracture. In the 2nd century AD, during the Roman Empire Era, Galen suggested trephination for depressed fractures, fractures with hematoma, comminuted fractures, and trichiasis (superficial gouging of the bone). In the Early Medieval Period, the increasing recognition of importance of anatomic barrier provided by skull and dura, lead to a decline in popularity of cranial surgeries. Despite this tendency, several examples of medieval neurosurgical skills have been demonstrated by archeological findings, originating from area of Italy and Hungary and dated for early to mid-middle ages (9–12). However, very little knowledge was added to the neurosurgical management of cranial injuries until the medical school in Salerno, Italy, regenerated interest in cranial surgery in the 11th century (13).

THE MASTERS

Berengario da Carpi (14)

Berengario da Carpi was an Italian physician and teacher of Anatomy at the Bologna University. After taking care of Lorenzo de' Medici, suffering from an occipital gunshot wound, he was inspired to write in 1518 "Tractatus de fractura calve sive cranei" (10). To our knowledge, the manuscript contains the first description of indications and technique of craniotomy. He reported three cases of brain injury successfully operated on, with 1 year follow up. One of these patients underwent also DC. He also reported a detailed description of surgical instruments and of the costs of the various procedures (**Figure 1**) (15).

EUGÈNE-LOUIS DOYEN (1859–1916): THE TEMPORARY HEMICRANIECTOMY

The first scientific reference and description of an hemicraniectomy was reported in 1896 by Charles Adrien Marcotte in his graduation thesis in Medicine and Surgery, named *De L'hemicraniectomie Temporaire* (16). The innovation of the *hemicraniectomie temporaire* consists of the realization of a large fronto-temporo-parietal bone flap (*volet osseux*), with the bone left adherent to periosteum, temporal muscle, subcutaneous tissues, and skin. The adhesion of the bone flap to the soft tissue would have limited wound defects, bone resorption and loss of substance (**Figure 2**) Although it was not used to treat severe TBI, the power of this technique in lowering increased intracranial pressure (i.e., in cases of meningitis) had already been introduced by Marcotte.

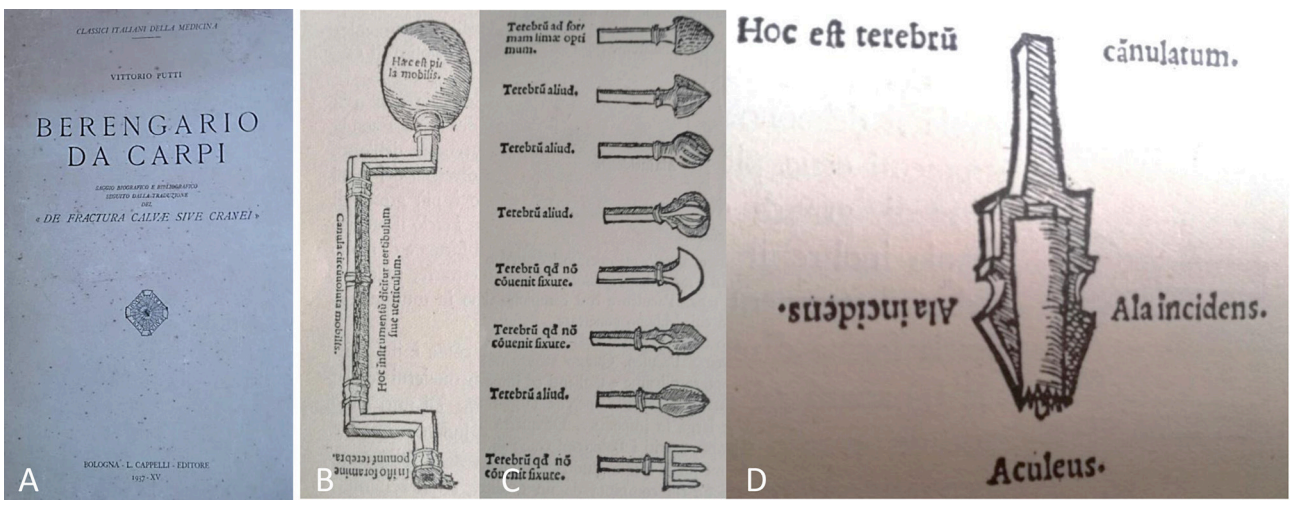
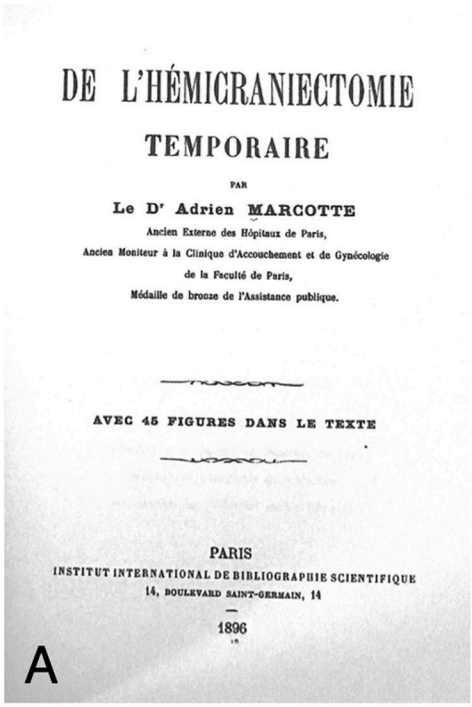


FIGURE 1 | (A) Frontispiece of De Fractura Calvae sive Cranei, original Italian translated copy (from *Vittorio Putti, Berengario Da Carpi "De Fractura Calvae sive Cranei", Bologna—L. Cappelli Editore, 1937, private collection.* Figure is in public domain and no permission is required for reuse). **(B–D)** These pictures show some of the surgical instruments in use at that time to perform a trephination.


DE L'HÉMICRANIECTOMIE
TEMPORAIRE
PAR
Le Dr Adrien MARCOTTE
Ancien Externe des Hôpitaux de Paris,
Ancien Moniteur à la Clinique d'Accouchement et de Gynécologie
de la Faculté de Paris,
Médaille de bronze de l'Assistance publique.
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PARIS
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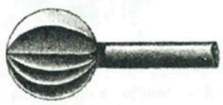
Fig. 78.


Fig. 79.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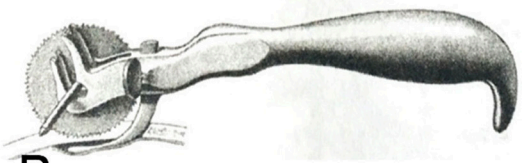
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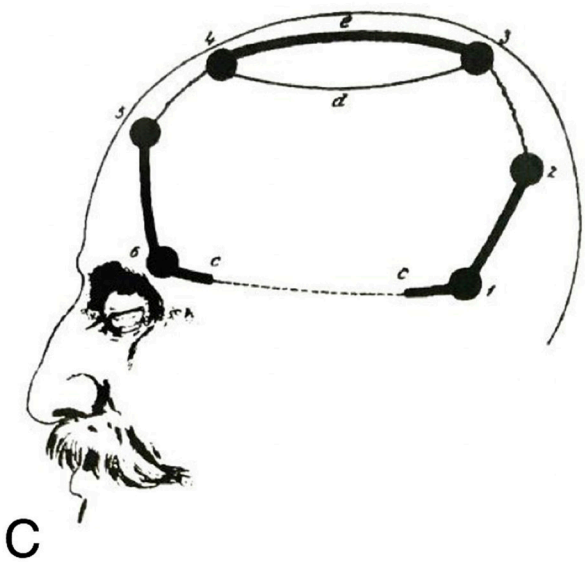
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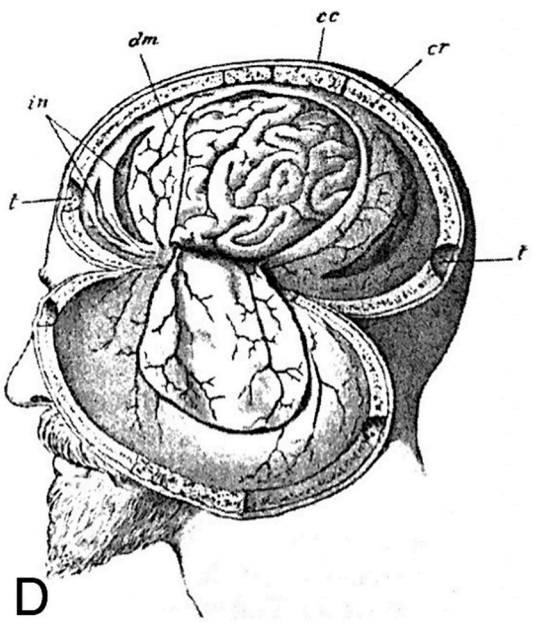


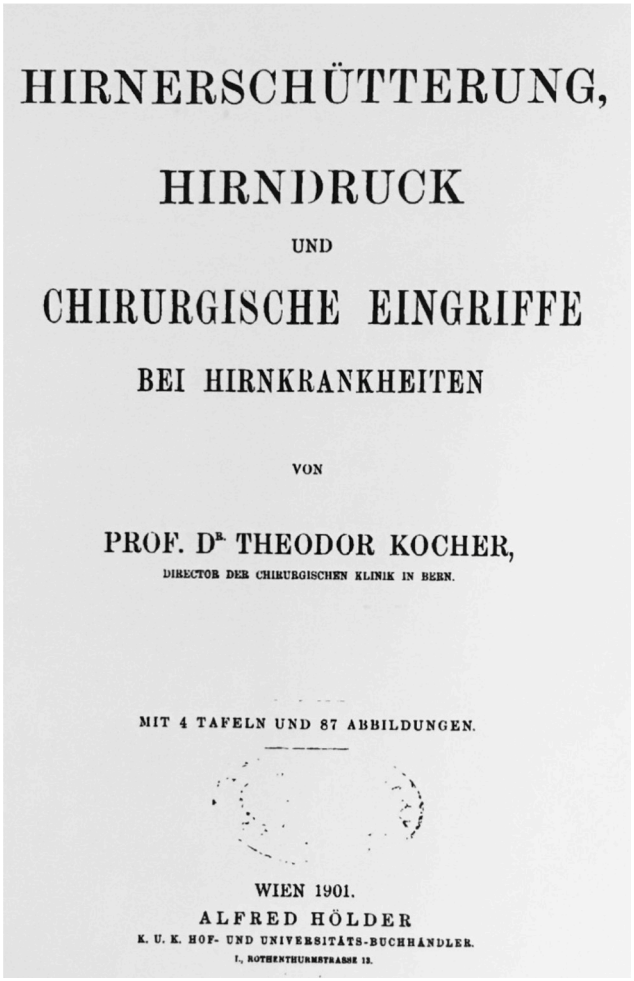
D

FIGURE 2 | (A) Frontispice of De l'hémicrniectomie temporaire, by Charles Adrien Marcotte. **(B)** Sample of the surgical instruments used by Doyen. **(C)** Lines and burr holes showing the extension of the temporary craniectomy. **(D)** Intradural view after performing temporary hemicraniectomy: the dural flap is usually downward overturned [from Marcotte (16). Figure is in public domain and no permission is required for reuse].

DC was described by Annandale in 1894 as a palliative procedure for inoperable brain tumors (17). Nevertheless, the most relevant experiences on DC in head trauma took place in the XX century.

Kocher and Cushing

The use of "large" DC for patients with raised intracranial pressure following TBI was firstly reported by Kocher in 1901. In his manuscript (**Figure 3**), he makes a systematic study of brain trauma and CSF circulation, and reported the therapeutic measures to be adopted in order to manage intracranial hypertension. In the Chapter VIII, he advocates the use of trephination, as soon as possible, in all cases of intracranial hypertension. In the Chapter XVIII he suggests to perform the temporary hemicraniectomy in selected cases where a pressure relief cannot be achieved by trephination alone (18).


HIRNERSCHÜTTERUNG,

HIRNDRUCK

UND

CHIRURGISCHE EINGRIFFE

BEI HIRNKRANKHEITEN

VON

PROF. Dr. THEODOR KOCHER,

DIRECTOR DER CHIRURGISCHEN KLINIK IN BERN.

MIT 4 TAFELN UND 87 ABBILDUNGEN.

WIEN 1901.

ALFRED HÖLDER

K. U. K. HOF- UND UNIVERSITÄTS-BUCHHÄNDLER.

I., ROTHENTHURMSTRASSE 13.

FIGURE 3 | Frontispiece of the manuscript by Dr. Theodor Kocher [from Kocher (18). Figure is in public domain and no permission is required for reuse].

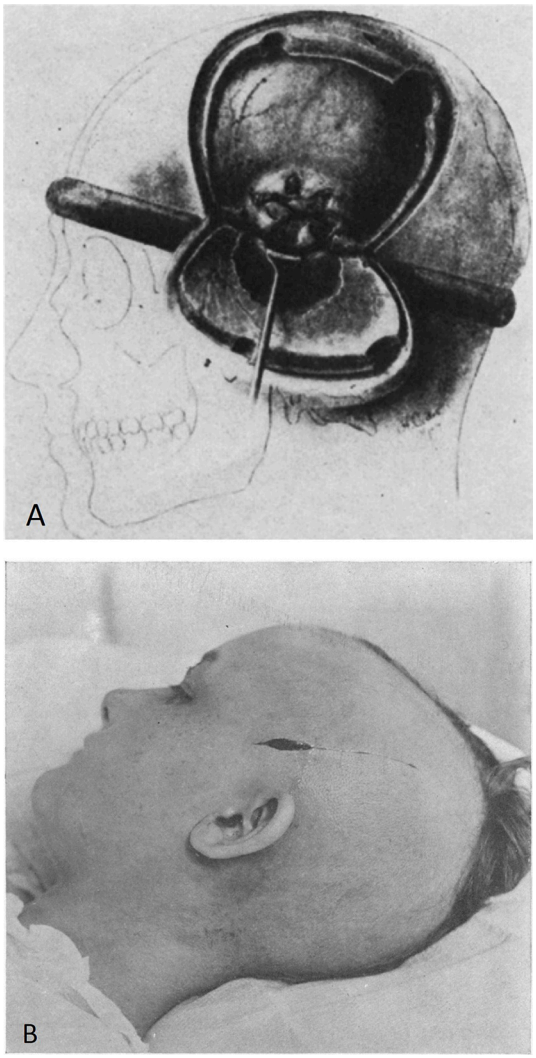


FIGURE 4 | (A) Decompressive measures described by Cushing for the management of cerebral hernia in inaccessible brain tumors [from Cushing (21). Figure is in public domain and no permission is required for reuse]. **(B)** Incision of the scalp for subtemporal craniectomy [from Cushing (20). Figure is in public domain and no permission is required for reuse].

From the lesson learned watching Kocher in Bern, US-neurosurgeon Cushing proposed DC for the treatment of other brain disorders (19–21).

In 1905, he reported the use of DC for inaccessible brain tumors (**Figure 4A**).

Only in 1908, he described the subtemporal DC for the intracranial complications associated with bursting fractures of the skull (20). The subtemporal craniectomy technique consisted of a linear incision of scalp, splitting of the fibers of the temporal muscle and a 4.5 cm diameter bone removal with dural opening (**Figure 4B**).

The immediate reduction of intracranial pressure had a favorable impact in reducing morbidity in survivors, compared with patients who did not undergo surgery (19, 20).

The indication by Cushing for decompressive craniectomy with aggressive wound debridement of fragments in penetrating brain injury followed his observation of 250 cases in War World I (22). The same recommendation was later supported by Matson, after analyzing World War II and Korean War head trauma data, and continued during the conflict in Vietnam (23). Cushing advocated watertight dural closure, a principle less valid in wartime nowadays. However, the DC in wartime goes beyond the scope of this paper and has been properly described elsewhere (24).

Hemicraniectomy, Bifrontal, and Subtemporal Craniectomy

After the preliminary experiences, clinical practice showed poor clinical outcomes. Therefore, DC quickly felt into discredit. From 1960 to 1980, only twenty-two papers dealing with DC in TBI were published, with a mean mortality rate from 46 to 96%, regardless of the surgical technique used (17, 25–34).

Two main techniques would have represented the standard during the next years.

The bifrontal craniectomy, reported by Kjellberg and Prieto in 1971, was performed in 50 patients with TBI. The main passages of the surgical technique are as follows: "*The reference points for the bone flap are: a burr hole over the frontal sinus; burr holes in the zygomatic portion of the frontal bone at the anterior insertion of the temporalis muscle; a burr hole 1 cm posterior to the coronal suture in the midline; and two burr holes laterally in the temporal region near the coronal plane of the midline burr hole. The burr holes are connected by a saw and the frontal bone removed, ordinarily in two halves. The dura is… incised bilaterally above the supraorbital ridges to the sagittal sinus anteriorly… The sinus and falx are divided by scissors*"

Kjellberg and Prieto did not think that this procedure was simply prolonging the life of patients with irreversible damage, but with proper indication could result in reasonable outcomes. They deplored its application in patients with modest injury, and noticed that younger survivors, even if they had a decerebrate state at presentation, had a better potential for good neurological recovery than the adults. They suggested "*the following indications as a guide to the decision to use this procedure: 1. Coma: totally unresponsive or responsive only to deep pain 2. Unilaterally or bilaterally dilated and fixed pupils 3. Apnea 4. Decerebrate posturing… at least two of the indications above should be present."* (30). In 1975, Venes and Collins made a retrospective analysis of 13 patients who underwent primary bifrontal DC for the management of post-traumatic cerebral edema. They reported a significant decrease in expected mortality (30.8%), but severe morbidity in the survivors, and only one 2 years-old patient completely recovered (34).

During the same year, Gerl and Tavan reported that extensive bilateral craniectomy with opening of the dura offers the possibility of rapid reduction of intracranial pressure. However, they observed 70% of mortality, and only 20% of the cases with full recovery (28).

The second technique is the evolution of the hemicraniectomy and would have represented the most popular mean of DC for several years. Ransohoff et al. reported their experience in thirty-five patients with "*unilateral acute subdural hematoma associated with predominantly unilateral underlying cerebral contusions and lacerations*." The authors referred a survival rate of 35%, with 7 patients returned to their normal occupation. According to these findings, hemicraniectomy seemed to show favorable results in patient with malignant cerebral edema, compared with previous series (33). The technique of hemicraniectomy by Ransohoff is described as follows: "*…a skin flap was extended from the glabella along the midline, terminating 4 cm above the external occipital protuberance. The skin incision was carried laterally to the level of the transverse sinus, and a one-layer skin flap including the periosteum was turned. A frontoparietal, occipital, and temporal bone flap was then removed to reveal almost the entire surface of the hemisphere… The temporal squama was rongeured to the floor of the temporal fossa, with the neurosurgeon making absolutely certain that no shelf of bone remained that might prevent subsequent lateral shift of swollen temporal lobe. The bone flap was discarded or placed in the bone bank. The dura was widely opened and hinged at the attachment of the superior sagittal sinus. Through this exposure it was possible to carry out a complete removal of all solid and liquid hematoma. The inferior surfaces of the frontal and temporal lobes were inspected for areas of clot and contusion....Bleeding from brain lacerations was controlled, and badly macerated brain was resected, if necessary. The bridging veins along the sagittal and transverse sinuses were inspected for active bleeding and were often found to be the source of the subdural hematoma. When hemostasis was satisfactory, the dura was laid over the surface of the brain, with no attempt at closure. … The scalp was closed in a one-layer on-end mattress technique...."*

The favorable effects of hemicraniectomy on limiting intracranial hypertension were also found in 1973 by Morantz et al. as well. The authors analyzed the radiological modification of midline shift in eleven patients with subdural or epidural hematoma underwent DC. In arteriograms, "*there was a general correlation between the degree of postoperative shift and the clinical status of the patient; the patients showing the best response displayed the least displacement of the midline structures and vice-versa."* (31).

THE END OF THE STORY?

In 1976, the experience of Cooper et al. seemed to establish the end of DC as a standard practice to limit the intracranial hypertension linked to the cerebral edema. He reported a 10% total and a 4% functional survival rate in 50 patients with TBI. No correlation with survival and patient's age, status of preoperative neurologic examination, angiographic findings, and appearance of the brain at operation was found (17, 35).

However, Cooper et al. recognized the value of DC only as a second tier treatment in deteriorating patients with no brainstem dysfunctions:

> "*The operation of hemicraniectomy should be restricted to those patients who enter hospital, obtunded but without demonstrable brain stem dysfunction, only to deteriorate subsequently because of increasing hemispheric edema and/or subdural clot*" (17).

THE DARK AGE OF DC

Despite the unfavorable results discouraged further investigations, some groups, particularly in Japan, continued to carry on research about the role of DC in TBI (36–38).

In 1979, Yamaura and Makino analyzed the effects of DC in patients with cerebral contusion. The authors stratified patients in different groups according to their age and the pre-operative clinical status (*key signs*: pupillary changes, decerebration and respiratory disturbance). Their findings were not different from previous studies: mortality rate was 23% in 0–29 vs. 40% in >30 years-old patients, and >30 years-old patients had poor functional recovery. Mortality was therefore lower in younger patients (36).

During the same years, Shigemori et al. published a short series of 15 patients with SDH treated with DC. Despite a poor post-operative outcome, the authors reported that the midline

shift and the ICP were not significantly modified in all patients with severe brain swelling, but mainly in the subgroup of patients with mild elevated intraoperative ICP (37).

However, some questions remained pending: (1) does the time from the traumatic event impact on mortality rate? (2) which is the pre-operative ICP value as a cut off for surgery and how does it relate to a favorable outcome? (3) Does pre-operative clinical status affect the post-operative outcome?

In 1980, Shishido et al. found that patients with lower ICP (10–30 mmHg) who underwent DC had a better post-operative neurologic status compared to patient with rapidly increasing post-operative ICP or with higher values (40–70 mmHg). This study showed how the ICP seemed to be a crucial element able to influence the response to therapy in patients with TBI and diffuse cerebral damage (38).

THE REBIRTH OF DC

The improvement of ICP monitoring techniques and the widespread adoption of therapies to reduce intracranial pressure, i.e., mannitol, hyperventilation, barbiturates, extended the care of post-traumatic intracranial hypertension to a multidisciplinary team, mainly composed by surgeons and neurointensivists. Indeed, it allowed to reduce the application of DC only to selected cases, with brain edema not responsive to medical treatment, as a second-tier therapy (39–44).

Moreover, the reported success of DC for stroke (45, 46) was also a factor contributing in renewing interest in DC for TBI.

According to this, in 1988 Gower et al. proposed a step-by-step treatment algorithm for patients with closed head injury. The authors examined 115 patients with severe closed head injury, with invasive monitoring of ICP, started on a regimen of medical treatment (head elevation, fluid restriction, chemoparalysis, hyperventilation at PCO2 25-30 torr and, if not responsive, mannitol). ICP above 20 mmHg triggered further therapeutic maneuvers including skull decompression. In the group of decompressed patients, 40% survived, compared with 82.4% of patients in pentobarbital coma group without decompression. Some important information came from this study: (1) the treatment of intracranial hypertension had to be guided by the ICP value; (2) the DC could be efficacious as second-tier therapy; (3) however, the mortality rate in the decompressed group was not changed yet if compared to the past (40).

In 1990, Gaab et al. with a prospective study design treated 37 patients <40 years old. They performed 19 bifrontal craniotomies and 18 hemicranietomies, and reported 5 deaths (13.5%), 3 vegetative states (8.1%), while all other patients achieved full social rehabilitation or remained moderately disabled; they established as best predictor of a favorable outcome an initial posttraumatic Glasgow coma scale (GCS) ≥7 (37).

Another interesting observation was described by Yamakami and Yamaura (44). They observed a significant relationship between the increasing of CBF, assessed by SPECT99m technetium-hexamethyl-propyleneamine oxime, recorded 24 h after DC, and an improvement of GCS score (40).

Between the end of 1990s and the first years of 20th century, some authors (47–52) tried to establish a new role for surgical bone flap decompression and duraplasty in the treatment of severe head injuries.

Polin et al. confirmed that timing had a positive impact on ICP control. Furthermore, pre-operative higher GCS (≥6) and younger age were positive predictor of good outcome (50).

In 1999, Guerra et al. conducted a prospective clinical study on the effect of bilateral or front temporal craniectomy in patient with refractory intracranial hypertension not responsive to medical therapy. Their results looked surprisingly good: only 11 patients (19%) died; five patients (9%) survived, but remained in a persistent vegetative state; six patients (11%) survived with a severe permanent neurological deficit, and 33 patients (58%) attained useful social rehabilitation. According to them, DC was

TABLE 1 | Differences between the RCTs by Taylor et al. (2) DECRA and RESCUEicp trials.

	Taylor et al. (2)	DECRA	RESCUE-icp
Recruitment up to 72 h post-TBI	100%	100% of patients	56% of patients
TBI type	Diffuse injury and/or mass lesions	Diffuse injury only	Diffuse injury and/or mass lesions (including contusions and evacuated hematomas)
ICP threshold	ICP 20–24 mmHg for 30 min, 25–29 mmHg for 10 min, 30 mmHg or more for 1 min	> 20 mmHg for 15 min in 1 h	> 25 mmHg for at least 1 h
ICP-lowering therapies before randomization	Tier 1	Tier 1	Tiers 1 and 2
Pooled mortality	33.30%	18.7%	37.5%
Mortality in DC vs. medical group	11.1 vs. 22.2%	19 vs. 18%	26.9 vs. 48.9%
Documented follow-up	6 months	6 months	6 and 12 months
Poor outcome (medical group vs. surgical group)*	86 vs. 46 %, $p = 0.046$^	51 vs. 70%, $p < 0.01$	65.4 vs. 57.2%, p = NS (6 months) 67.7 vs. 54.6%, $p < 0.01$ (12 months)

From Kolias et al. (59) used and modified with permission.

^The modified Glasgow Outcome Score (GOS) to obtain a functional outcome.

**In the DECRA trial, the upper sever disability (patient independent only at home) was considered among the poor outcomes, in the RESCUEicp trial, in view of the indication to surgery as last tier, it was considered as good outcome.*

indicated in patients <50 years-old, with brain swelling on CT scan, no fatal primary brain injury, before irreversible brainstem damage or generalized ischemic brain damage (monitoring of ICP, and B wave, AEPs, & SEPs) had occurred (48).

In 2000, Munch et al. assessed how unilateral DC could modify ICP, CPP, and few CT parameters like brain shift and status of the mesencephalic cisterns. DC was performed as primary-tier therapy in 63.3% and as secondary-tier therapy in 36.7% patients. Despite a significant reduction of midline shift, this finding did not correlate with a better patient outcome, that was favorable in only 41% patients (49). Differently from the results by Polin, timing seemed not to be related to patient's outcome, as confirmed by Whitfield and Guazzo (52).

Thanks to these authors, we understood that DC was effective in improving brain elasticity, reducing ICP, improving CBF and overall survival, but not the functional status.

In summary, at the end of the 20th century, the indications for DC were the following: ICP >30–35 mmHg or CPP<45–70 mmHg, age <50 years, GCS>4, CT signs of brain swelling, associated masses, GCS 3 plus bilateral fixed pupils excluded (48, 50–52). Two conditions for DC were already indicated even if not well-defined yet: primary, if associated with haematoma evacuation (49); secondary, if followed ICP increase not treatable with medical therapy (48, 50–52).

The main conclusions drawn from the few studies dealing with the role of DC in post-traumatic diffuse brain injury were: (1) decompression had to be performed in selected cases, mainly young patients with GCS not inferior 7 and without signs of irreversible brain damage, only after failure of intensive medical care; (2) timing, age and post-operative ICP could have a significant impact on post-operative outcome; (3) the therapy had to be focused on maintaining a stable ICP (<20 mmHg); (4) despite the surgical and anesthesiological advances, the outcome of operated patients did not substantially improve. The number of patients with a good recovery or a moderate disability was still about 30%.

However, at that time no randomized controlled trials had been still carried on.

THE ERA OF RANDOMIZED TRIALS

During the 21st century, DC in TBI has become very popular again, with a striking increase in the number of published papers.

Most of these papers are single or multi-center retrospective series, case reports and reviews (53–58).

Until now, three randomized controlled trial (RCT) have been carried on and one (RESCUE-ASDH trial) is ongoing. The trials differ in terms of study population: inclusion criteria, methods and outcome (**Table 1**), (1–3) and criticisms have been raised, for example in terms of the inclusion criteria for the DECRA trial (60–63). Kolias et al. have recently compared and discussed the DECRA and RESCUEicp trials (59).

In conclusion, current evidences from multicenter clinical trials suggests that early neuroprotective bifrontal DC for mild to moderate intracranial hypertension is not superior to medical management for patients with diffuse TBI. DC used as a last-tier therapy for patients with severe, sustained, and refractory posttraumatic intracranial hypertension leads to a substantial mortality reduction but increases disability compared to medical management. However, at 12 months there was a significant difference in the number of patients with a favorable outcome (defined as upper severe disability—independent at home for at least 8 h) compared to the medical management (3, 64, 65).

LESSONS FROM THE PAST: *ERRARE HUMANUM EST PERSEVERARE AUTEM DIABOLICUM (TO MAKE MISTAKES IS ACCEPTABLE, BUT NOT TO REPEAT THEM…)*

The technique of DC as a therapy to reduce ICP has ancient roots. We have learned from the past that DC is an extreme measure, not a panacea for any case of increased ICP. Indeed, a significant percentage of survivors have moderate to severe neurological sequelae. Therefore, decisions to recommend DCs must always be made not only in the context of "*its clinical indications but also after consideration of an individual patient's preferences and quality of life expectation*" (66).

AUTHOR CONTRIBUTIONS

All the authors meet the 4 criteria according to the ICMJE (International Committee of Medical of Medical Journal Editors). In detail, ZR and FS had a substantial role in designing and drafting the paper. AK and PH significantly contributed to the analysis, interpretation critically revising the work. FN and PD equally contributed to the acquisition and interpretation of data.

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MINI REVIEW
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Role of Decompressive Craniectomy in the Management of Cerebral Venous Sinus Thrombosis

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Cerebral venous sinus thrombosis (CVST) is a relatively uncommon cause of stroke more often affecting women and younger individuals. Blockage of the venous outflow rapidly causes edema and space-occupying venous infarctions and it seems intuitive that decompressive craniectomy (DC) can effectively reduce intracranial pressure just like it works for malignant middle cerebral artery infarcts and traumatic brain injury. But because of the relative rarity of this type of stroke, strong evidence from randomized controlled trials that DC is a life-saving procedure is not available unlike in the latter two conditions. There is a possibility that other forms of interventions like endovascular recanalization, thrombectomy, thrombolysis, and anticoagulation, which cannot be used in established middle cerebral artery infarcts and TBI, can reverse the ongoing pathology of increasing edema in CVST. Such interventions, although presently unproven, could theoretically obviate the need for DC when used in early stages. However, in the absence of such evidence, we recommend that DC be considered early as a life-saving measure whenever there are large hemorrhagic infarcts, expanding edema, radiological, and clinical features of impending herniation. This review gives an overview of the etiology and risk factors of CVST in different patient populations and examines the effectiveness of DC and other forms of interventions.

Keywords: anticoagulation, cerebral venous sinus thrombosis, decompressive craniectomy, outcome, risk factors

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INTRODUCTION

Cerebral venous sinus thrombosis (CVST) is a stroke caused by blockage of cortical veins and dural venous sinuses which leads to infarction of the draining zone brain parenchyma. It manifests as headache (in 75–95% of cases), seizures, papilledema, altered consciousness, and focal neurological deficits (1–4). CVST is the least common form of acute cerebrovascular disease, accounting for just 0.5% of all types of stroke (5–7). However, this figure rises to 15% of all young strokes in the Asian population (8, 9). The commonest site of origin of thrombosis is believed to be the junction of cerebral veins and larger sinuses (10). Several disorders can cause or predispose patients to CVST such as genetic and acquired prothrombotic disorders, cancer, hematological diseases, vasculitis, systemic inflammatory disorders, pregnancy, puerperium, and infections. In addition, there are a number of local causes such as brain tumors, arteriovenous malformations, basilar skull fracture,

CNS infections, and extracranial infections like those arising from the ear, sinus, mouth, face, or neck (11–14). Medical or surgical conditions that increase the likelihood of deep vein thrombosis also increase the risk of intracranial venous thrombosis. In the international prospective study on the cerebral vein and dural sinus thrombosis (ISCVT), 44% of the patients had >1 risk factors. Congenital or genetic thrombophilia was present in 22% of patients. In about 13% of adult CVST patients, despite an extensive search, no underlying risk factors could be found (15). More than 90% of the CVST occurs in people below 60 years of age and it is more commonly seen in women between 20 and 35 years. Young women have a higher risk due to pregnancy, puerperium, and oral contraceptive usage (16–20). The incidence of CVST is estimated to be 1–13 cases per 100,000 per year (5, 16, 21). The incidence in neonates and children is 0.67 cases per 100,000 children, and that of perinatal CVST is 11.6 per 100,000 deliveries in pregnant women (16, 22, 23).

DECOMPRESSIVE CRANIECTOMY IN CVST

Indications

About 4% of the patients develop supratentorial parenchymal hemorrhagic lesions and cerebral edema severe enough to cause brain herniation and deterioration in neurological functions (8). The term "malignant CVST" is often used to designate this entity (24). Although anticoagulation to promote recanalization by preventing thrombosis progression is considered the mainstay of CVST treatment, it is insufficient to treat the ongoing mass effect of a malignant CVST (24). When aggressive medical management fails to control the raised intracranial pressure, DC is needed to mitigate the deleterious effects of cerebral herniation (**Figures 1A–C**).

We recommend that DC is offered as early as possible when the patients develop clinical signs (such as a third nerve palsy) and radiological features of herniation due to large or expanding hemorrhagic or edematous infarcts (**Figure 1D**). Radiological features that prompt consideration of DC are large uncal herniation, midline shift $\geq$5 mm, and herniation induced hypodensity of the posterior cerebral artery territory. When it is anticipated that aggressive medical management is likely to fail and if there is insufficient time for anticoagulation to act by facilitating recanalization, DC should be done. Such a policy helps reduce the chances of herniation induced irreversible brain stem damage and posterior cerebral artery infarcts which can occur without much warning. In less severe cases, where there is no gross evidence of herniation, a trial of standard intensive care management of raised ICP with ventricular CSF drainage, osmotic agents, and transient hyperventilation may be done. Where there is uncertainty, the decision can be guided by ICP monitoring, but the insertion of a parenchymal or ventricular device must be done with normal coagulation parameters. Persistent ICP levels above 20 cm of CSF despite conservative management should also prompt consideration for DC (**Figure 1D**).

Surgical Technique

A sufficiently large, unilateral hemicraniectomy, ideally centered on the site of the largest hematoma and venous infarct, allows expansive duraplasty with homologous or artificial material to reduce ICP. We believe that the recommendations for a large hemicraniectomy of 15 cm or greater for middle cerebral artery infarcts should also hold true for CVST since the reduction in ICP is the primary effect of DC. Infarcts affecting both anterior frontal lobes may be better dealt with using a bifrontal craniectomy, although there are no trials comparing both techniques. Evacuation of infarcted tissue is generally not recommended. However, spontaneous rupture of infarcts that typically occur at the site of dural opening warrants its removal. Medical management of cerebral edema should be continued in the postoperative period and may also be guided by ICP monitoring. There are as yet no definitive guidelines for ICP monitoring either before or after DC. The bone flap should be replaced once the brain swelling has subsided and this usually takes 3–6 months. We believe that cranioplasty should be done as early as reasonably possible to reduce the risk of complications of DC like subdural effusions, sunken skin flap syndrome, and hydrocephalus.

Since CVST is a rare cause of stroke and because of the ethical difficulties in delaying or not offering decompression when there is an obvious mass effect, large double-blinded randomized controlled studies seems difficult to conduct (25). Though the quality of evidence is low (Class IIb; Level of Evidence C), the intuitive need to perform DC in CVST is strong in select circumstances (6, 21). Meta-analysis and well-conducted systematic reviews combining data from multiple centers are useful when randomized controlled trials are unavailable. Unfortunately, even such studies evaluating the role of DC in CVST are sparse. Almost 10 years back, Coutinho et al. (26) and Lanterna et al. (27) independently published two reviews based on three previously published cases each where DC for large venous infarcts led to good outcomes. In the ISCVT study (28), the largest evaluation of its kind in CVST, 624 adult patients were registered. Most of the investigators of the trial were neurologists and only nine patients (1.4%) had a surgical intervention (29). Due to the low numbers of patients who underwent surgery, the role of DC was not analyzed. Seven years later, in 2011, the same investigators reviewed the role of DC with a combined retrospective registry and systematic review of 69 patients in 22 centers who had a surgical evacuation (30). During the last follow-up (median: 12 months), 15.9% of patients died and 5.8% of patients were severely dependent. The corresponding figures in their first report, wherein only 1.4% had undergone DC ($n = 624$) were 8.3 and 2.2%. Given the fact that only patients with malignant CVST underwent surgery (nine in ISCVT, 69 in the 2011 systematic review), the differences were comparable.

Over the years, multiple small observational studies suggest that surgery improves survival and produces acceptable outcomes even in patients with severe clinical conditions (8, 25, 30–32). The average death rate among patients treated with DC was 18.5%. The complete recovery rate was 30.7% and severe dependency rates were only 3.4% (21). The benefits are

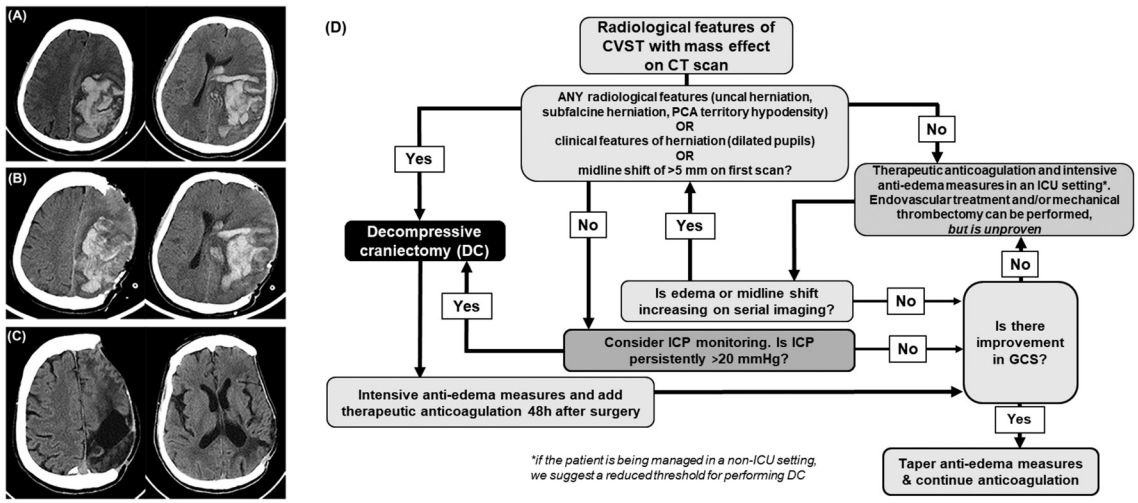

FIGURE 1 | Cerebral venous sinus thrombosis (CVST). **(A)** Computed tomography depicts a confluence of blotchy areas of bleed typically seen in hemorrhagic CVST with mass effect. **(B)** Day 1, and **(C)** 8 months, post decompressive craniectomy. **(D)** Flowchart outlining the management of CVST. CT, computed tomography; ICU, intensive care unit. GCS, Glasgow coma scale; ICP, intracranial pressure.

thought to be not only due to the prevention of progression of herniation but is also attributed to an improvement in the cortical venous collateral drainage that happens with the reduction in raised intracranial pressure. Unlike arterial infarcts, the variable patterns of apparent diffusion coefficient maps in MRI suggest that even large venous infarcts have a far better potential for recovery (24). Even in comatose patients and those with bilateral fixed pupils, DC seems beneficial, and leads to a good recovery in about one-third (8, 24) (**Figure 1D**).

Zuurbier et al. in a prospective cohort study of 10 DC patients reported a good clinical outcome in six patients, while two died (31). Aaron et al. (33), in a single center retrospective study on 44 patients undergoing DC reported a good outcome in 27 patients (61.4%) while nine patients died (20%). Theaudin et al. (24) retrospectively studied 12 patients with malignant cerebral edema out of 255 patients with CVST. All the four non-operated patients died, and all but one of the seven patient who underwent surgery survived and improved neurologically. The six survivors had a modified Rankin score (mRS) of 0 or 1 at 1 year. Authors also recommend that resection of infarcted tissue was not justified given the potential for recovery of venous infarction and suggests selective removal of large hematomas alone (24). Mohindra et al. in a retrospective study of 13 patients who underwent DC, reported a good outcome in all the 11 patients who survived. The two patients in their series who did not survive had a preoperative GCS <5 (34). In another retrospective study by Zhang et al. (32) of 58 patients who underwent DC, 46.6% had hemorrhage-dominated lesions and 56.9% had edema-dominated lesions. At 6 months, 56.9% of the patients attained a favorable outcome, while 13.8% died. Hemorrhage-dominated lesions and deep venous involvement cases had poorer outcomes.

We reviewed studies which were published after the last systematic review in 2011 by Ferro et al (30). Medline, PubMed, Google Scholar were used to identify studies reported in the English language with combinations of the following search terms: "cerebral sinus thrombosis," "venous thrombosis," and "craniectomy." Only those studies which evaluated more than 15 patients who underwent DC and had follow-up assessment, were selected. **Table 1** shows studies (2012 till the present) which evaluated the role of DC in CVST. Most of the single-center, high-volume studies were published from low-to-middle income countries, and includes two from the author's institution [see **Table 1**; (35, 37)] and it reflects the prevalence of uncorrected nutritional anemia and deficient perinatal care in general. Though endovascular services are available at the author's institution, DC was often required because the majority of the patients presented with impending herniation where the role of thrombolysis was limited. A total of 169 patients underwent DC for CVST in five studies and the mortality rate was 16.1%. A favorable outcome, defined as complete recovery or slight disability (mRS of 0–2, GOS of 5), could be calculated from three studies ($n = 136$) and such an outcome was achieved in 54.4% of the patients at the end of the follow-up period. Pre-operative ICP monitoring to guide the management plan was used only in one study but its effectiveness in decision making was not analyzed. Four studies favored DC in CVST with large hemorrhagic lesions causing midline shift and radiological features of intracerebral herniation. The results of our review are consistent with that by Ferro et al where mortality of 15.9% and a favorable outcome of 56.5% were reported. In addition to the obvious limitation that none of the studies had survival data from a control group who were managed conservatively, other shortcomings include the variations in the protocols employed, the myriad ways those protocols could have been escalated while the patients were being managed conservatively in different centers and the bias that is inherent to all retrospective uncontrolled studies. As mentioned before, the major strength of the present mini-review is that it

TABLE 1 | Major studies evaluating the role of decompressive craniectomy in cerebral venous sinus thrombosis published after the systematic review in 2011[a].

References	Type of study	Subjects (N[b])	Study period	Mean GCS	Basis for DC[c]	Mean follow up (months)	Outcome	Comments
Ferro et al. (30)	Systematic review, multicentric registry and review	69[d]	1998–2010	NA	Large hemispheric lesions and poor GCS	14.5	11 died. 39 patients recovered to mRS[7] score 0 1 or 2.	Recommend DC
Vivakaran et al. (35)	Retrospective single center study	34	2006–2008	8.3	Clinical deterioration, Herniation syndrome	11.7	Four died. 14 recovered patients with GOS five	Recommend DC
Aaron et al. (33)	Retrospective single center study	44	2002–2011	NA	Volume of lesion and midline shift	25.5	Nine died. Three lost to follow up. Twenty seven patients had mRS core 0, 1 or 2	Recommend DC
Soyer et al. (36)	Retrospective single center study	16[e]	2002–2005	NA	Clinical deterioration. ICP monitoring was used in 8 patients	28	Five died during hospital stay. A detailed outcome assessment in treatment groups was lacking	For a similar CVST severity, craniectomy did not improve the outcome
Zhang et al. (32)	Retrospective single center study	58	2005–2015	6.7	Clinical deterioration, Herniation syndrome	6	Eight died. Thirty three patients attained a favorable outcome (mRS score of 0 in three patients, score of 1 in 13, and score of 2 in 17)	Recommend DC
Venkateswaran et al. (37)	Prospective cohort study	17	2015–2016	9 (median)	Clinical deterioration midline shift	18.6	One died. Two lost follow ups. Median mRS score of 1.5 in 14 patients	Improvement in regional cerebral oxygen saturation with DC

[a] *Only studies with a number of decompressive craniectomies more than 15 were selected.*
[b] *N stands for the total number of patients who underwent DC.*
[c] *Only the predominant reasons for DC are given in the table.*
[d] *Number of patients in the registry were 38, and 31 in Review: 45 patients underwent DC and the rest underwent other procedures.*
[e] *Total cases in the study were 47. DC, decompressive craniectomy; mRS, modifed Rankin score; CVST, cerebral venous sinus thrombosis.*

included all the major studies till date which were published after the last systematic review in 2011.

ANTICOAGULATION IN CVST

In 1941, Lyons reported the first successful use of unfractionated heparin in two cases of cavernous sinus thrombosis (9). Presently, anticoagulation with hydration is the first-line treatment for CVST. Anticoagulation prevents propagation of the thrombus, hastens its spontaneous resolution, and aids in the prevention of deep vein thrombosis and embolism, without adversely promoting intracranial hemorrhage (ICH) (2, 19, 25, 38). ICH is not considered a contraindication for anticoagulation (9). Unfractionated heparin has to be given intravenously and it requires a dose adjustment based on activated partial thromboplastin time. Low-molecular-weight heparin (LMWH) is advantageous in that it can be administered as a subcutaneous injection based on body weight, and it has a more predictable pharmacokinetic profile (21) (**Table 2**). However, its effects are only partially reversed with protamine sulfate. The quality of evidence is too low to choose between the agents (21). LMWH is associated with lesser risk of new hematomas and seems to have better outcomes in ISCVT trial and other studies (25, 39, 40). It can be given in patients with normal renal function and those who do not require neurosurgical intervention (16, 39).

The time to restart therapeutic anticoagulation after DC is not clear (41, 42). Previous studies suggest that anticoagulation can be restarted after 24 to 48 h and some authors prefer to start with half the dosage for a period of 72 h (25, 31–33). Permanent anticoagulation is needed in those with prothrombotic states or with recurrent venous thrombosis (43). Other patients can be treated with oral Vitamin K antagonists for a period of 3–12 months (21, 44). There is limited safety data for oral anticoagulants such as Apixaban (45).

Systemic administration of fibrinolytic agents such as urokinase to recanalize thrombosed pathways has been attempted but strong evidence regarding its safety and efficacy is lacking (9). Endovascular thrombolysis may also be considered in patients who are unresponsive and deteriorating, despite aggressive medical treatment (10). Siddiqui et al., in their

TABLE 2 | Summary of various treatment modalities for CVST.

Treatment modality	Treatment methods	Comments
Anticoagulation	Intravenous • Unfractionated heparin • Low-molecular-weight heparin	The first line of treatment for CVST.
Fibrinolysis	Intravenous /Endovascular • Streptokinase • Urokinase	Small case series and prospective studies without a control group are available. Efficacy and safety are not established.
Thrombectomy	Endovascular • Mechanical thrombectomy • Suction thrombectomy • May be combined with fibrinolysis	Only a limited number of studies published. Further controlled trials are required to establish benefit.
Surgical intervention(s)	Open surgical thrombectomy	Few published case reports. With increasing access to endovascular modalities, microsurgical removal of thrombus is probably not indicated.
	Decompressive craniectomy	Class IIb; Level C Evidence. Indications include: 1. Clinical and radiological signs of herniation. 2. Persistently raised ICP refractory to medical management.

CVST, cerebral venous sinus thrombosis; ICP, intracranial pressure.

systematic review assessing mechanical thrombectomy with or without intrasinus thrombolysis suggested that this approach is safe (46). The overall death or dependency rate was 16% in patients who underwent mechanical thrombectomy, even though 47% of patients in this series were comatose or stuporous. The rate is comparable to that in the ISCVT study and indicates the safety of the approach (46). In cases where DC has no reasonable immediate role due to the absence of a life-threatening mass effect, patients may benefit from endovascular interventions (28, 47). Thrombolysis or anticoagulation for Cerebral Venous Thrombosis (TO-ACT trial) (48) study which sought to evaluate the role of endovascular thrombolysis was prematurely terminated due to futility.

DECOMPRESSIVE CRANIECTOMY IN CVST IN DIFFERENT AGE GROUPS

Pregnancy

Only case reports are available which describe DC in pregnant women. Patients might require a cesarean section for the safe delivery and resuscitation of the neonate (49). Puerperal CVST is more common and can be severe enough to warrant DC as a life-saving measure. Most of the studies indicate that future pregnancies are not contraindicated in women with a previous history of CVST (50). The absolute risk of recurrent venous sinus thrombosis associated with pregnancy in women who had a previous episode of CVST seems to be low, although the relative risk is much higher than the rate in the general population (50). Regardless of antithrombotic prophylaxis, the pooled estimate for recurrent CVST and non-cerebral venous thromboembolism associated with pregnancy was 9 per 1,000 pregnancies and 27 per 1,000 pregnancies, respectively (51). The avoidance of oral contraceptives and the use of anticoagulation prophylaxis during pregnancy dramatically reduced the probability of thrombosis recurrence in women (52).

Pediatric CVST

In a study based on a Canadian pediatric stroke registry, neonates comprised of 43% of the children diagnosed with CVST, and 54% were younger than 1 year old (23). The increased risk in the neonates is attributed to multiple reasons such as the damage sustained by dural venous sinuses secondary to the molding of the skull bones during delivery, general prothrombotic state and dehydration (25). Infection is a major cause for CVST in children, and hypoxia is also thought to play a significant role in neonates (6, 23). Treatment with anticoagulants is generally considered to be safe, although studies are few (25, 53). In children over 2 years of age, a duration 3 to 6 months of anticoagulation should be tailored according to the cause (54). The indications and risk-benefit analysis of DC in pediatric CVST are not clear. DC is generally thought to be risky in neonates and young infants but may be cautiously considered in older children (55).

CVST in the Elderly

CVST tends to be equally prevalent in older men and women. A headache as a presenting symptom is less common in the elderly (56). CVST should thus be added to the long list of disorders that cause depressed consciousness or mental changes in patients, and an extensive search must be done for such causes. In ISCVT, 8.2% of the patients were aged 65 years or older (22). The prognosis was worse with 49% of patients being dead or dependent at the end of the follow-up period. Due to an increased risk of thrombotic events, anticoagulation for more than 6 months may be warranted.

OUTCOME

CVST has a favorable outcome when compared with other types of stroke. Due to increasingly early diagnosis and the widespread use of anticoagulation, the outcomes have been better than what existed half a decade ago (25, 57). The overall death rate is below 5% and about 80% of the patients make a complete recovery (mRS scores: 0–1) (21, 25, 38). However, mortality in severe cases with parenchymal lesions still remains as high as 35–50% (16, 50, 58). In ISCVT, 3.4% of patients died within the first month of thrombosis, 6.8% after 6 months and 8.3%, at the last follow up (median follow-up 16 months). Moderate to severe disability was reported in 5.1% of the patients (32). The role of recanalization of thrombosed veins in relation to the outcome is not very well established (39, 59, 60). In ISCVT, the main predictors of mortality within 30 days were male gender, age more

than 37 years, seizure, mental status disturbance, GCS score <9, deep CVST, central nervous system infection, posterior fossa lesions and malignancy (8, 24). Patients older than 50 years, midline shift of more than 10 mm, total effacement of basilar cisterns, deep venous involvement, and bilateral lesions imply a poorer outcome in patients who underwent DC (8, 32).

CONCLUSIONS

We recommend DC in select patients with medically intractable mass effect and raised intracranial pressure where herniation is an immediate risk. In less severe cases, therapeutic anticoagulation with LMWH and medical management of raised ICP seems reasonable. A large decompressive flap like the one recommended for middle cerebral artery infarcts for predominantly unilateral lesions or a bifrontal craniectomy for bifrontal infarcts are the surgical options.

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RA wrote, edited and reviewed the manuscript. MG wrote and edited the manuscript. BD edited, critically reviewed the manuscript. DB and DS reivewed the manuscript. NS edited, reviewed the manuscript and prepared figures. All authors approved the final version.

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Chapter 12: Decompressive Craniectomy: Long Term Outcome and Ethical Considerations

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Decompressive craniectomy (DC) for the treatment of severe traumatic brain injury (TBI) has been established to decrease mortality. Despite the conclusion of the two largest randomized clinical trials associating the effectiveness of decompressive craniectomy vs. medical management for patients with traumatic brain injury (TBI), there is still clinical equipoise concerning the usefulness of DC in the management of refractory intracranial hypertension. Primary outcome data from these studies reveal either potential harm or that decreased mortality only leads to an upsurge in survivors with severe neurologic incapacity. In this chapter, we seek to review the results of the most recent clinical trials, highlight the prevailing controversies, and offer potential solutions to address this dilemma.

Keywords: outcomes—health care, decompressive craniecotmy, intracranial hypertension, medical ethics, traumatic brain injury (craniocerebral trauma)

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BACKGROUND

Averting cerebral hypoxia and hypotension as well as subsequent secondary injury are the key aims of management following severe traumatic brain injury (TBI). Cerebral ischemia can occur through reduced autoregulation after neural insults leading to disturbance of the usual homeostatic mechanisms (1). This can result in a malicious sequence of amplified intracranial hypertension, reduced cerebral blood flow, and metabolic derangement (2, 3). As intracranial pressure continues to increase, subsequent cerebral herniation can result in poor patient outcomes (4).

Decompressive craniectomy (DC), the surgical removal of a portion of the skull, has been used for many years in patients with TBI (5). In patients with raised intracranial pressure (ICP), DC has been described to increase cerebral perfusion and oxygenation leading to enhanced clinical outcome in patients with intractable hypertension (6, 7).

The controversy in the role of DC in severe TBI stems from the contradictory results of the latest randomized controlled trials (RCTs) (8–12). Some proponents against DC for TBI suggest it may simply increase the subset of subjects who survive but remain neurologically non-functional with subsequent poor quality-of-life (11, 13). Opinion varies concerning the operating techniques used in patients undergoing DC. Over the past 30 years, several clinical investigations and observational studies have tried to address this through examining craniectomy size, craniectomy vs. craniotomy, and surgery time (14–18). Thus, despite the conclusion of the two largest RCTs comparing the efficacy of DC vs. medical management for patients with TBI, there is still clinical equipoise regarding the roll of DC in the management of refractory ICH (11, 12).

EXISTING RANDOMIZED CLINICAL TRIALS—DECRA AND RESCUEicp TRIALS

"The Early Decompressive Craniectomy in Patients With Severe Traumatic Brain Injury" (DECRA trial) RCT, associated bifronto-temporo-parietal DC to primary medical management for refractory ICH, with refractory ICP defined *as >20 mm Hg within an hour window for >15 min*. The investigation employed subjects in 15 tertiary care hospitals in three countries between 2002 and 2010 (12). The DC group included 73 patients and the medical management group included 82. The study found inferior scores with regard to Extended Glasgow Outcome Scale (GOS-E), for subjects if enrolled for DC, despite these patients having had lower ICP and fewer ICU days, than for those having received standard care at 6 months post-injury. Mortality at 6 months for DC was 19% vs. for medical management 18% for medical management (not statistically significant) and GOS-E showed a trend toward worse outcomes if enrolled for DC. Limited inclusion criteria, including the threshold for refractory ICP (ICP > 20 for 15 min within a 1-h period), raised inquiries regarding the generalizability of the results (12).

"The Randomized Evaluation of Surgery with Craniectomy for Uncontrollable Elevation of Intracranial Pressure" (RESCUEicp) sought to resolve these issues. The inclusion criteria were refined to include subjects with intracranial mass lesions of the traumatic subtype. In addition, the definition of refractory ICP was re-defined as *>25 mm Hg between 1 and 12 h in duration* (11). On subject presentation, radiographic imaging was reviewed and stratification for either single-sided or bilateral craniectomy based on the clinical judgment of the surgeon. Subjects enrolled in the medical treatment arm could receive further barbiturates as needed to dampen ICP. If continued clinical worsening occurred, subjects could also cross-over and receive a subsequent decompressive craniectomy. Six months GOS-E was utilized as the primary outcome. Twelve months GOS-E was the secondary outcome. This RCT remarkably revealed improved ICP and better mortality rates overall. There was a notable increase in the subset of patients with poor GOS-E, a score usually associated with poor quality of life.

While results from the RESCUEicp trial established an improvement in mortality for DC at 6 months, they also displayed increased rates of vegetative state and disability than medical care.

TABLE 1 | DECRA vs. RESCUEicp trial comparison.

	DECRA	RESCUEicp
Surgical group	73	202
Medical group	82	196
Age (years)	15–60	10–65
Number tertiary centers	15	52
Duration study (year)	2002–2010	2004–2014
Surgical proecedure	Bilateral	Bilateral or Unilateral
Criteria for DC	ICP > 20 mmHG, within 1h, for >15 min	ICP > 25 mmHg, between 1 and 12 h
Duraton follow up	6 months	24 months

Of note, the investigation also completed a subsequent analysis looking at the percentage of subjects that had GOS-E scores between 4 and 8. This patient subset was deemed as "favorable" as they would be independent at home or better. At 6 months, there were no significant differences between the GOS-E scores between the DC and medically treated subjects (42.8 and 34.6%, respectively; $P = 0.12$), but when looking at the 12-months data, a significant trend toward benefit from DC begins to emerge (45.4 vs. 32.4%; $P = 0.01$) (11). A comparison of DECRA and RESCUEicp is found in **Table 1**.

ETHICAL CONSIDERATIONS FOR PATIENTS AND FAMILIES: SURVIVAL WITH UNFAVORABLE OUTCOME

Grounded on the current clinical data using primary outcome measures ranging only to 6 months, it would seem that utilization of DC for TBI can be a lifesaving intervention. The major concern however, is that this surgical choice may merely save lives at the expense of existence with severe disability and, thus, a poor quality of life (19, 20).

Survey studies have been initiated on patients who have experienced DC in the context of stroke, investigated their outcome satisfaction and whether surgery would have been acceptable initially. If their reply was generally affirmative, this answer would surmise retrospective consent (21). In one study, 28 patients were followed after undergoing DC to assess long-term outcomes. Retrospective consent to DC was achieved in roughly four out of five patients. Notably they mention that patients that achieved modified Rankin scores of four or better tended to provide retrospective consent (21). A conceivable explanation of these outcomes may be that these patients were able to adapt to and accept their neurologic disability. Indeed, quality of life perceptions are ultimately patient specific, with perceptions of whether life is perceived to be "worth living" is dependent on the individual context (22).

It is important to have patients discuss their life-support preferences with their health care delegates. Shared decision making should be emphasized regarding medical and surgical options, possible outcomes from involvement, and truthful quality of life goals following recovery. Patients should be aware that if they are not able to provide consent at the time of a severe TBI with no health care proxy available, then surgery may be performed at the discretion of the surgeon/health care team.

FUTURE CONSIDERATIONS: UTILIZATIONS OF LONG-TERM OUTCOME DATA

The current clinical trial results strongly suggest the disadvantages of restricting follow up to <1 year. The lack of encouraging clinical evidence to back the use of DC in TBI may be, in part, due to the use of 6-months primary outcome data. This is especially relevant in the context of severe TBI, as

patients often require extended time (12–24 months, or more) for functional recovery.

There is evidence of an advantage to using long term outcome metrics to evaluate the role of DC for TBI. Investigations, however are limited only to retrospective cohort studies, as RCTs to date have only published up to 12-months outcome data. Of the studies that address longer-term follow up, there have been notable improvements in outcome (23, 24). One study found in a cohort not included in the DECRA trial, that roughly half of patients ($N = 176$) had a one-point improvement in the GOS-E score between 6 and 18 months after DC. Of the 59 patients that had unfavorable outcome 6 months following surgery (defined as severe disability or worse), 25% ($n = 15$) improved to favorable outcome (defined as moderate disability or better) at 18-months follow up (23). Another investigation found an 11.6% significant increase in favorable outcome between three months and 2 years follow up ($n = 60$) (24).

In other neurosurgical literature, the utility of RCT's with long-term follow up has shed light in guiding the treatment paradigm for patients presenting with ruptured intracranial aneurysms. Notably, the 9-years outcome data for the International Subarachnoid Aneurysm Trial (ISAT) helped address the controversy of aneurysm stability treated with endovascular intervention, with long term follow-up results demonstrating that the risk of re-bleeding with this intervention was low (25).

TBI symptomatology may persevere for decades harming cognitive capabilities and psychosocial functioning, advocating for looking at quality of life (QoL) outcomes for a duration of more than the standard 3 years in order to obtain accurate clinical results (26). There is also a subset of patients whose outcomes may worsen over time due to structural impairments of the brain, progression of brain atrophy and microstructural changes (27). We recognize the barriers faced by the authors of the DECRA and RESCUEicp trials when conducting their respective large scale RCTs in regards to the restrictive fiscal barriers imposed by RCT subsidy (28). However, we propose that it is a necessity to include funding for 12–36 months follow-up to support research coordinators and data management. Furthermore, it may be of benefit to streamline outcome variables in order to mitigate patient attrition and to utilize web-based techniques to streamline follow up (29).

CONCLUSIONS

In spite of the conclusion of the two largest RCTs equating the efficacy of DC compared to medical management for patients with TBI, the recommendations and indications for the use of DC in the context of refractory ICH remains highly debatable. The DECRA study displayed no advantage from early bifrontal surgical DC to reduce ICP in diffuse TBI, though the applicability of the results were questionable owing to restrictive inclusion criteria. The RESCUEicp trial brought a new perspective to these issues by including more frequently encountered patient conditions and by raising the threshold for refractory ICH (>25 mm Hg for 1–12 h). The RESCUEicp trial showed that DC in patients who failed initial treatment measures was associated with lower mortality than in patients who underwent medical management. However, at 6-months, a greater number of subjects in the DC arm than in the medical treatment arm, were in a vegetative state or reliant on others for activities of daily living.

While these results may underscore the belief that improvements in mortality from emergent lifesaving procedures do not necessarily correlate with enhancements in quality of life, there is concern for relying solely on 6-months primary outcome measures to define the effectiveness of a treatment for a condition (severe TBI) that demonstrates ongoing recovery for 12–24 months, or longer. Careful evaluation of the 12-months outcome for RESCUEicp suggests improvement in the DC cohort given that the upper severe disability group, by definition, had partial independence at home. Twenty-four months follow-up is anticipated to be published after the data is examined. However, the conclusions thus far argue for greater inspection in selecting the criteria of patients chosen for DC and for enhancement in diagnosis and treatment through further investigation and technological innovation.

It is worth noting that discussions regarding decompressive craniectomy should also include the optimal timing of cranioplasty (replacement of the bone flap or artificial substitute) to restore then normal anatomy of the cranium. Risks of prolonged trephanation may include focal neurological deficits, or stored bone flap erosion. Hydrocephalus and extra-axial hygromas can occur due to altered cerebrospinal fluid dynamics. Unfortunately an optimal time of cranioplasty has not yet been delineated but early cranioplasty has been shown to result in shorter operative times and decrease costs (30).

Due to the complicated discussions regarding patient outcomes and quality of life goals, it is unlikely that a single algorithm can be followed to guide patients and their families through the difficult sequela of TBI. Additionally, the ethical concerns may also vary based on the unique cultural beliefs, faiths and medical economics of the patient's geographic location. Regrettably, the acute clinical setting in which these matters need to be deliberated is inadequate and psychologically stressful. However, it is necessary to have early, comprehensive discussions with families regarding the risks and benefits of treatment. These conversations should take into account the potential prognosis for recovery and, whenever possible, include the patients' prior wishes and tolerance for disability.

AUTHOR CONTRIBUTIONS

KK and JS both performed research and wrote the text. JU, the senior author, conceived of article theme, guided structure, and edited manuscript.

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The Role of Decompressive Craniectomy in the Context of Severe Traumatic Brain Injury: Summary of Results and Analysis of the Confidence Level of Conclusions From Systematic Reviews and Meta-Analyses

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Introduction: Traumatic brain injury (TBI) is a global epidemic. The incidence of TBI in low and middle-income countries (LMICs) is three times greater than in high-income countries (HICs). Decompressive craniectomy (DC) is a surgical procedure to reduce intracranial pressure (ICP) and prevent secondary injury. Multiple comparative studies, and several randomized controlled trials (RCTs) have been conducted to investigate the influence of DC for patients with severe TBI on outcomes such as mortality, ICP, neurological outcomes, and intensive care unit (ICU) and hospital length of stay. The results of these studies are inconsistent. Systematic reviews and meta-analyses have been conducted in an effort to aggregate the data from the individual studies, and perhaps derive reliable conclusions. The purpose of this project was to conduct a review of the reviews about the effectiveness of DC to improve outcomes.

Methods: We conducted a systematic search of the literature to identify reviews and meta-analyses that met our pre-determined criteria. We used the AMSTAR 2 instrument to assess the quality of each of the included reviews, and determine the level of confidence.

Results: Of 973 citations from the original search, five publications were included in our review. Four of them included meta-analyses. For mortality, three reviews found a positive effect of DC compared to medical management and two found no significant difference between groups. The four reviews that measured neurological outcome found no benefit of DC. The two 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 one study that measured it, and a significant reduction in hospital length of stay in the two studies that measured it. According to the AMSTAR 2 criteria, the five reviews ranged in levels of confidence from low to critically low.

Conclusion: Systematic reviews and meta-analyses are important approaches for aggregating information from multiple studies. Clinicians rely of these methods for concise interpretation of scientific literature. Standards for quality of systematic reviews and meta-analyses have been established to support the quality of the reviews being produced. In the case of DC, more attention must be paid to quality standards, in the generation of both individual studies and reviews.

Keywords: brain injury, head trauma, decompressive craniectomy, ICP, TBI

INTRODUCTION

Traumatic brain injury (TBI) remains one of the most serious public health problems worldwide, and in particular in low- and middle-income countries (LMICs) (1). Decompressive craniectomy (DC) has been used for the management of intracranial pressure (ICP) with severe TBI patients as a primary or prophylactic intervention, or as a secondary intervention when first-line therapies fail (2–4). Some studies in TBI populations have shown that DC improves ICP and cerebral perfusion pressure (CPP), contributing to improved long-term functional outcomes and reduction in costs (5–12). However, other studies show opposite results (13–15). Given the variation in results, leading to uncertainty about the actual benefit or not of the procedure, multiple systematic reviews and meta-analyses have been conducted to synthesize the results of the individual studies. However, in order to use the information from these reviews to make treatment and policy decisions, the findings must be critically considered within the context of the quality of the reviews.

Standards have been established for the assessment of the quality of systematic reviews and meta-analyses. One instrument that is widely used is AMSTAR 2 (A MeaSurement Tool to Assess systematic Reviews) (16). The instrument contains 16 individual domains, with 7 of them being "critical domains." It was developed to provide health professionals and policy makers with a practical critical appraisal instrument to assess systematic reviews and meta-analyses that include randomized controlled trials (RCTs) as well as non-randomized studies (NRSs).

We conducted a literature search to identify systematic reviews and meta-analyses that compare the outcome for patients with severe TBI who receive DC with patients who receive standard medical management. We used the AMSTAR 2 instrument to assess the included publications. The purpose of this project was to summarize the findings of the publications in light of their AMSTAR 2 scores, and to identify potential improvements in the conduct of systematic reviews about DC that could contribute to the confidence in the findings. Thus, the emphasis in this paper is to critically assess the included systematic reviews/meta-analyses.

MATERIALS AND METHODS

The search included systematic reviews (SRs) and meta-analyses (MAs) published on the topic of DC in the treatment of severe TBI patients. A search strategy was developed including mesh terms and all field terms but also free text searches in search engines. The main strategy included: "brain injuries, traumatic"[MeSH Terms] OR "craniocerebral trauma"[MeSH Terms] AND ("decompressive craniectomy"[MeSH Terms] OR "decompressive craniectomy"[All Fields]) OR "decompressive craniotomy"[All Fields], filtering by study types of meta-analysis and systematic review (excluding all other types of studies). Systematic reviews/meta-analyses that included pathologies other than TBI, and those that focused on interventions other than DC specifically, were excluded.

Two investigators independently reviewed abstracts and full text articles. Discrepancies were resolved through consensus of three investigators.

RESULTS

Literature Review

Nine hundred seventy three citations were obtained, most of which were not specific to the topic or did not meet the inclusion criteria. Six publications were retrieved that met the pre-determined inclusion criteria (17–22). We eliminated Sahuquillo (17) because it included only one study (23), which was included also in four of the other included reviews (18, 20–22). Thus, five SRs/MAs were included in this review.

The five reviews included 9 RCTs and 16 NRSs (see **Table 1**). Four of the five studies included both RCTs and NRSs, and one (21) included only RCTs. Three of the five studies used only RCTs in their MAs (18, 20, 21), one included both RCTs and NRSs in the MA (22), and one did not conduct a MA (19).

Assessment of Individual Reviews

The following summarizes each review with an emphasis on findings from the MA (when utilized) and RCTs, and presents the results of the AMSTAR 2 assessments.

Wang et al. (18) conducted a SR and MA to investigate the effect of early DC on mortality, ICP reduction, and hospital stay. They included three RCTs and five NRSs in their review, and used only the RCTs for the MA (see **Table 1**). For mortality, the pooled odds ratio (OR) was 0.531 [95% confidence interval (CI) 0.209–1.350, $Z = 1.95$, $p = 0.183$]. There was a significant reduction in ICP for the DC group compared to the non-DC group (pooled difference in means −2.081, 95% CI −2.796 to −1.366, $p < 0.001$). Also, the DC group had significantly fewer days in hospital than the non-DC group (pooled difference in means −9.907, 95% CI −16.250 to −3.565, $p = 0.002$). Thus, the findings from the pooled analysis indicate no significant effect

TABLE 1 | Summary of systematic reviews/meta-analyses about decompressive craniectomy.

Publication	Population and intervention	RCTs	Non-randomized studies	MA	Results	AMSTAR 2
Wang et al. (18)	Early DC for severe TBI	(5, 14, 23)	(13, 24–27)	Yes for RCTs	Half the risk of death for DC group, but not statistically significant. ICP and hospital stay significantly lower for DC group.	Critically low. Violation of five and partial violation of one of the seven critical domains.
Barthélemy et al. (19)	DC and alternative means of decompression for severe TBI	(14, 28–30)	(31–38)	No	No difference in mortality or neurological outcomes between DC and medical management. Significantly better mortality and neurological outcomes for DC with multiple dural stabs compared to DC with open dural flap.	Low. Violation of two of the seven critical domains.
Zhang et al. (20)	DC for severe TBI	(5, 14, 23, 39)	(13, 24–27, 40)	Yes for RCTs	DC group had significantly lower mortality, ICP, and length of ICU and hospital stay than medical management group. DC group had significantly more complications. No significant difference in neurological outcomes between groups.	Low. Violation of one and partial violation of three of the seven critical domains.
Sahuquillo and Dennis (21)	DC for severe TBI	(14, 23, 41)	None included	Yes for RCTs	DC reduces the risk of mortality compared to medical management. DC does not reduce the risk of unfavorable outcomes.	Low. Violation of two and partial violation of two of the seven critical domains.
Fatima et al. (22)	Early DC for severe TBI	(14, 23, 41–43)	(26, 44)	Yes for all studies	Significantly lower risk of mortality with DC than with medical management ± late DC. No difference in neurological outcomes between early DC group compared to medical management ± late DC. Significantly lower risk of mortality with early DC than with late DC, but no difference in neurological outcomes.	Critically low. Violation of four and partial violation of one of the seven critical domains.

RCT, randomized controlled trial; DC, decompressive craniectomy; ICP, intracranial pressure; MA, meta-analysis.

of DC on mortality, and significantly reduced ICP and days in hospital.

Applying the AMSTAR 2 assessment criteria, the confidence in the findings from this review is critically low. They sustained violations in 5 of the 7 critical domains, and a partial violation for one additional critical domain (see **Table 2**).

Barthelemy et al. (19) conducted a SR of studies that compared DC to medical management or to alternative means of surgical decompression, and reported on mortality, neurological outcomes measured by the Glasgow Outcome Scale (GOS), and ICP. The alternative means of decompression included craniotomy with controlled decompression and DC with multiple dural stabs (MDS). Four RCTs and eight NRSs were included in the review (see **Table 1**), which did not utilize a MA to combine data. Thus, the reported results and conclusions were derived from findings from the individual studies, rather than from pooled quantitative data. Among the RCTs, no significant benefits were found in mortality or neurological outcomes between the DC group and the medical management group, or between the DC group and the controlled decompressive craniectomy group. One study (28) found significantly lower mortality and higher function at discharge for patients who received MDS compared to DC. Of the two trials that reported on ICP, one (29) showed no benefit of DC and one (14) showed significant reduction in ICP with DC.

The AMSTAR 2 rating for this review is low confidence. There were violations in 2 of the 7 critical domains (see **Table 2**).

Zhang et al. (20) conducted a SR and MA to compare DC to medical management, and reported on mortality, neurological outcomes measured by the GOS, length of stay in the intensive care unit (ICU), length of stay in hospital, and complications. Of the ten included studies, four were RCTs and six were NRSs; the RCTs were included in the MA (see **Table 1**). For mortality, patients in the DC group had significantly lower risk of death compared to patients who received only medical management [Risk Ratio (RR) 0.59, 95% CI 0.47–0.74, $Z = 4.60$, $p < 0.001$]. Subgroup analysis showed a significant benefit for mortality with the early DC group ($p < 0.001$) but no difference for late DC ($p = 0.89$). For neurological outcomes, no significant difference was found between groups on the GOS or GOS-E (Extended GOS) at 6 months follow-up (RR 0.85, 95% CI 0.61–1.18, $Z = 0.97$, $p = 0.33$). However, the subgroup analysis of early DC showed a significant benefit in neurological outcome compared

TABLE 2 | AMSTAR 2 individual domains and overall confidence scores for systematic reviews/meta analyses about decpompressive craniectomy.

Review criteria	Publications				
	Fatima et al. (22)	**Sahuquillo and Dennis (21)**	**Zhang et al. (20)**	**Barthélemy et al. (19)**	**Wang et al. (18)**
1. Did the research questions and inclusion criteria for the review include the components of PICO?	Yes	Yes	Yes	Yes	Yes
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	No	Partial yes	No	No	No
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Yes	Yes	Yes	Yes	Yes
4. Did the review authors use a comprehensive literature search strategy?	Partial yes	Yes	Yes	Yes	Partial yes
5. Did the review authors perform study selection in duplicate?	Yes	Yes	Yes	Yes	Yes
6. Did the review authors perform data extraction in duplicate?	No	No	Yes	No	No
7. Did the review authors provide a list of excluded studies and justify the exclusions?	No	No	Partial yes	No	No
8. Did the review authors describe the included studies in adequate detail?	Yes	Yes	Yes	Yes	Yes
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	No	Partial yes	Yes	Yes	No
10. Did the review authors report on the sources of funding for the studies included in the review?	No	No	No	No	No
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	No	Yes	Yes	N/A	Yes
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	Yes	Yes	No	N/A	No
13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	Yes	Yes	Partial yes	Yes	No
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes	No	Yes	Yes	Yes
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Yes	No	Partial yes	N/A	No
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes	No	Partial yes	Partial yes	Partial yes
Overall confidence	Critically low	Low	Low	Low	Critically low

Shaded rows indicate critical domains.
RoB, risk of bias.

to late DC (RR 0.74, 95% CI 0.56–0.99, $Z = 2.02$, $p = 0.04$). Compared to medical management, DC significantly reduced ICP [mean difference (MD) −2.12 mmHg, 95% CI −2.81 to −1.43, $Z = 6.03$, $p < 0.001$]; significantly reduced length of ICU stay (MD −4.63 days, 95% CI −6.62 to −2.65, $Z = 4.57$, $p < 0.001$); and significantly reduced length of stay in hospital (MD −14.39 days, 95% CI −26.00 to −2.78, $Z = 2.43$, p=0.02). The DC group sustained significantly more complications than the medical management group (RR 1.94, 95% CI 1.31–2.87, $Z = 3.33$, $p = 0.0009$). In sum, the DC group had significantly lower mortality, ICP, and length of ICU and hospital stay than the medical management group, and had significantly more complications. There was no difference between groups in neurological outcomes.

The AMSTAR 2 rating for this review is low confidence. There was a violation of 1 of the 7 critical domains, and partial violations of 3 critical domains.

Sahuquillo and Dennis (21) limited their SR and MA to only RCTs comparing DC to medical management. They reported on mortality and neurological outcomes measured by the GOS-E. Three trials were included in the review. Pooled results indicated significantly lower mortality for the DC group compared to the medical management group (RR 0.61, 95% CI 0.48–0.78, $I^2 = 38\%$). There was no significant difference between groups in neurological outcome measured at 6 months follow-up (RR 1.08, 95% CI 0.93–1.20, $I^2 = 78\%$). Authors reported DC was superior to medical management in reducing ICP, but did not provide quantitative data. To summarize, this review found that DC reduces the risk of mortality compared to medical management, reduces ICP, and does not reduce the risk of unfavorable neurological outcomes.

The AMSTAR 2 rating for this review is low confidence. There was violation of 2 of the 7 critical domains, and partial violation of 2 of the critical domains.

Fatima et al. (22) conducted a SR and MA to compare outcomes from early DC with those from medical management with or without (±) late DC. They reported on mortality and neurological outcomes measured by the GOS. Of seven included reviews, five were RCTs and two were NRSs (see **Table 1**). All studies were included in the MA. There was significantly lower mortality for the early DC group compared to the medical management ± late DC group (RR 0.62, 95% CI 0.40–0.94, $p = 0.03$). There was no difference between groups for neurological outcomes (OR 1.00, 95% CI 0.75–1.34, $p = 0.99$). A subgroup analysis indicated a significant reduction in mortality for the early DC group compared to the late DC group (RR 0.43, 95% CI 0.26–0.71, $p = 0.0009$), but no difference in neurological outcomes (OR 1.30, 95% CI 0.75–2.27, $p = 0.35$). In sum, when early DC is compared to medical management ± late DC, there is a significantly lower risk of mortality with early DC but no difference in neurological outcomes; the findings are the same in subgroup analysis that compares early DC to late DC.

The AMSTAR 2 rating for this review is critically low. They sustained violations in 4 of the 7 critical domains and a partial violation in 1 of the critical domains.

TABLE 3 | AMSTAR 2 scoring system.

High–Zero or one non-critical weakness: The systematic review provides an accurate and comprehensive summary of the results of the available studies that address the question of interest

Moderate–More than one non-critical weakness*: The systematic review has more than one weakness, but no critical flaws. It may provide an accurate summary of the results of the available studies that were included in the review.

Low–One critical flaw with or without non-critical weaknesses: The review has a critical flaw and may not provide an accurate and comprehensive summary of the available studies that address the question of interest.

Critically low–More than one critical flaw with or without non-critical weaknesses: The review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies.

**Multiple non-critical weaknesses may diminish confidence in the review and it may be appropriate to move the overall appraisal down from moderate to low confidence.*

Summary of the Findings From the Five Reviews

For mortality, three reviews found a positive effect of DC compared to medical management and two found no significant difference between groups. The four reviews that measured neurological outcome found no benefit of DC. The two 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 one study that measured it, and a significant reduction in hospital length of stay in the two studies that measured it.

Subgroup analyses showed the following: early DC reduced mortality compared to late DC, but did not improve neurological outcomes in one study; in another study, DC was associated with significantly more complications; in a third study that assessed alternative means of decompression, dural stabs improved mortality and neurological function compared to open dural flap.

Summary of the Quality of the Reviews Based on AMSTAR 2

The scoring system for the AMSTAR 2 instrument is in **Table 3**. As stated earlier, there are 16 domains that constitute the instrument, with 7 designated as "critical domains." The shaded columns in **Table 2** are the critical domains for the instrument.

According to the AMSTAR 2 criteria, the five reviews ranged in levels of confidence from low to critically low. The most common violations were in critical domain #2, "Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?" and in critical domain #7, "Did the review authors provide a list of excluded studies and justify the exclusions?" None of the reviews adhered completely to these criteria. Other violations include inadequate investigation of publication bias (domain 15) and insufficient technique for assessing risk of bias (domain 9). In light of the AMSTAR 2 scores for these reviews, confidence in the reported findings is low.

DISCUSSION

As stated in the Introduction, the purpose of this project was to summarize the findings from SRs and MAs about the effectiveness of DC to improve outcomes for patients with severe TBI, and to consider those findings in the context of their AMSTAR 2 scores. In general, the reviews report that DC can decrease mortality, reduce ICP, and minimize days in the ICU and hospital, but does not serve to improve neurological function. However, based solely on the AMSTAR 2 criteria, we report a low level of confidence in these findings. They are in part, however, consistent with findings from Class 1 RCTs (14, 41). These RCTs, as well as other literature about DC, have been the focus of intense and ongoing critical conversation (39, 45, 46), and have inspired the gathering of a formidable group of clinical experts who generated a consensus statement about DC (39).

DC is a complex and multi-faceted intervention. A key flaw in DC studies and reviews has been a lack of sufficient attention to this complexity in the conduct the studies and the analyses. Cranial decompression is a procedure with several technical variations (primary vs. secondary, early vs. delayed, bifrontal vs. unilateral). Furthermore, timing of the DC is a source of heterogeneity within and across studies. The SRs and MAs mixed these variations in the DC intervention in pooled analyses.

The findings for the effect of DC on mortality from the five SRs/MAs included in this review were mixed; three found a positive effect and two found no difference between groups. However, all four SRs/MAs that measured neurological outcomes concluded no benefit from DC. To consider this finding, we focus on the factor of the timing of the DC procedure from the two Class 1 trials included in this review—DECRA (14) and RESCUEicp (41). Both trials aimed to treat patients with refractory elevated intracranial pressure. The median time from injury to surgery in the DECRA trial was 38.1 h [interquartile range (IQR) 27.1–55.0]. Timing for the RESCUEicp trial was reported as follows: time from injury to initial treatment: <12 h. $N = 120$, >12 h. $N = 76$; median time from initial treatment to randomization 44.3 h (IQR 16.8–80.9); median time from randomization to surgery 2.2 h IQR 1.3–5.1, mean 7.5 h (95% CI 5–9.9). Thus, the timing of the DC procedure in these trials ranged from hours to days, being technically studies of secondary DC.

Some neurosurgeons believe that DC is best performed as a last ditch procedure, as it is drastic and it has a high complication rate. However, in the setting of potentially intractable ICP, perhaps the delay in timing—meant to be a conservative approach—is at least in part a source of the observed poor outcomes. Are poor outcomes an inevitable result of delayed surgery, and overly conservative surgical approaches? To date, a trial of early DC with a pre-specified, controlled surgical approach has not been conducted. Such a trial could run the risk of over-aggressive use of DC. The next step might be a systematic review and report of the evidence for patient and injury characteristics that are indicators of the need for immediate surgery; then a trial randomizing this subset of patients to DC or medical management.

Timing is only one factor that varies across studies, and is used here as an example of the possible sources of study and SR/MA heterogeneity.

CONCLUSION

Systematic reviews and meta-analyses are important approaches for aggregating information from multiple studies but are susceptible to misinterpretation of the results due to methodological flaws. Clinicians rely on these methods for concise interpretation of scientific literature. Standards for assessing SRs and MAs have been established to support the quality of the reviews being produced. In the case of DC, more attention must be paid to quality standards, in the analysis of both individual studies and reviews. In the included reviews, the procedure was found to decrease mortality, reduce ICP, and minimize days in the ICU and hospital, but was not found to improve neurological function. However, according to the assessment of the reviews utilizing a validated instrument, these conclusions have a low level of confidence.

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AR, NC, AK, and MA contributed equally to the conception, writing, and preparation of the manuscript.

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REVIEW
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Cranioplasty Following Decompressive Craniectomy

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Cranioplasty (CP) after decompressive craniectomy (DC) for trauma is a neurosurgical procedure that aims to restore esthesis, improve cerebrospinal fluid (CSF) dynamics, and provide cerebral protection. In turn, this can facilitate neurological rehabilitation and potentially enhance neurological recovery. However, CP can be associated with significant morbidity. Multiple aspects of CP must be considered to optimize its outcomes. Those aspects range from the intricacies of the surgical dissection/reconstruction during the procedure of CP, the types of materials used for the reconstruction, as well as the timing of the CP in relation to the DC. This article is a narrative mini-review that discusses the current evidence base and suggests that no consensus has been reached about several issues, such as an agreement on the best material for use in CP, the appropriate timing of CP after DC, and the optimal management of hydrocephalus in patients who need cranial reconstruction. Moreover, the protocol-driven standards of care for traumatic brain injury (TBI) patients in high-resource settings are virtually out of reach for low-income countries, including those pertaining to CP. Thus, there is a need to design appropriate prospective studies to provide context-specific solid recommendations regarding this topic.

Keywords: cranioplasty, decompressive craniectomy, traumatic brain injury, cranial reconstruction, bone flap, posttraumatic hydrocephalus

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INTRODUCTION

The operative surgery of therapeutic decompressive craniectomy (DC) for traumatic brain injury (TBI) involves the elevation of a free cranial convexital bone flap that is stored either *in vivo* (e.g., abdominal or thigh subcutaneous pouches) or in *ex vivo* mediums (deep freezing and tissue banking) (1, 2). Skull defects can result from direct trauma or postsurgical craniectomy. Varying shapes, sizes, and complexities of the defect can be observed.

Cranioplasty (CP) after DC aims to restore esthesis (3), improve cerebrospinal fluid (CSF) dynamics, and provide cerebral protection. In turn, this can facilitate neurological rehabilitation and potentially enhance neurological recovery (3). Although regarded as a routine neurosurgical procedure, CP can be associated with significant morbidity (4, 5).

This paper is a narrative mini-review rather than a systematic review. Therefore, a full search strategy is not provided; rather, we mainly focused on articles in the English language published in PubMed during the last 15 years.

SURGICAL TECHNIQUES

Although surgically straightforward, CP can lead to intraoperative complications at every operative step (elevation of the scalp flap, dissection of soft tissue from the underlying dura, and filling of the defect with a congruent rigid structure) (6, 7).

Required for flap elevation, the vascular territory of the flap must be kept in mind while performing the incision. Following an inner ellipse of the previous DC-surgery scar could contribute in most cases to the preservation of the vascular perfusion even if an incision outside of the ellipse might be needed in certain settings such as sinking skin flap syndrome (SSFS).

In patients where the skin may not be enough to cover the CP, due to an SSFS or skin lesions or scars, a single- or staged skin expansion procedure should be indicated.

However, most commonly, the operative dissections for CP after DC is performed by just opening the skin incision for the previous DC to develop the scalp flap for the CP.

The primary cranial damage control surgery is executed mainly by means of a unilateral frontotemporoparietal DC. This calls for a thoughtful consideration of the temporalis muscle (8), which is often found shrunken or inferiorly retracted toward its origins and adherent to the overlying scalp flaps and/or the underlying dura. This entails a delicate separation that can result in significant bleeding with a resulting increase in operative time. Other complications are intraoperative dural tears, cortical vascular, and parenchymal injuries, postoperative CSF wound leakage, as well as surgical site infections (SSI).

A number of techniques during the DC can potentially reduce the risks associated with the step of dissection. Some are preemptive techniques, such as the interposition of non-absorbable materials between the dura and the scalp flap during the primary DC and tagging the temporalis muscle with brightly colored, non-absorbable sutures for improved identification (9, 10).

COMPLICATIONS

Routine CP is known to have a higher rate of postoperative complications than other elective cranial procedures (11), which may appear at any point during the clinical course due to various factors both directly and indirectly related to the CP itself.

Walcott et al. reported that previous reoperation, comorbid disease type, presence of a ventriculoperitoneal (VP) shunt, and general cardiovascular risk factors are predictors of complications of CP post-DC after stroke and trauma (12). Additionally, skin flap complications such as dehiscence, ulcers, and necrosis are reported (13) and may be related to the exposure of subjacent tissues, always occur after CP in unilateral craniectomy, and preferentially affect the temporoparietal region. However, no correlation has been found between the biomaterials used and skin complications. Dehiscences occur essentially due to poor preoperative conditions, such as in chronically sunken flaps. Ulcers were always associated with an underlying infection and were rarely observed in craniectomized patients before undergoing CP. Necrosis was ascribed to inadvertent sacrifice of the residual arterial supply after flap reopening or to a venous congestion.

Infection

De Bonis et al. showed a 2.5-fold increased infection risk with a bifrontal CP compared with hemispheric/bihemispheric CP (14), regardless of the bone flap substitution material used. This is due to a longer incision and operative time, less temporalis muscle soft tissue coverage, and possible breaching of frontal sinuses during DC. Polymethylmethacrylate (PMMA) as the CP biomaterial shows significant infection rates when in contact with the nasal sinus mucosa or contaminated material (15). Hydroxyapatite (HA) implants (16) showed the highest incidence of infection (3.8%) in bifrontal defects. Also, a study of patients with titanium CP concluded that bifrontal insertion was one of the most relevant risk factors, with a complication rate of 40% including infections (17).

Following CP infection, the decision to remove a biomaterial is a complex issue and should be addressed in concert with plastic surgeons, especially when poor preoperative conditions of skin flap are observed. Even patients in good clinical conditions are at risk of sudden and/or further deterioration. Although, CP infection is rarely associated with sepsis, it is usually addressed by bone or implant removal until complete healing of the surgical field is achieved.

One possible way to address these issues of infection following CP is the development of new prosthetic biomaterials capable of resisting microbial colonization.

Hydrocephalus (HC)

After DC, the occurrence of ventriculomegaly (VM) or HC is reported with varying incidences (10–45%) mainly due to differences in diagnostic criteria (18–21). The management of HC in patients in need of cranial reconstruction can be challenging and thus is not precisely defined. The debate mainly revolves around the timing of CSF diversion with respect to the CP.

Nasi et al. (22) reported 28.4% occurrence of HC in a series of 130 DC at 6.43 postoperative months. In 91.9% of patients, a ventriculoperitoneal shunt (VPS) was required, 76.4% of which was implanted after CP, 14.7% synchronous with, and only in 8.8% before the cranial reconstruction.

The disappearance of VM after CP is well-documented (23–25), and the postoperative management strategy of an unnecessary VPS placement (26–28) is yet unclear. In patients with a bulging scalp flap and VM, external CSF drainage achieved *via* ventriculostomy or lumbar drainage could allow an accurate repositioning of CP without brain damage.

The use of programmable shunts for patients dependent on CSF shunt has been effectively proven in various case series (29–31). Nevertheless, in socioeconomic environments with limited resources, a fixed pressure valve remains often the only option.

MATERIAL TYPES

Autologous Bone

With few exceptions, autologous bone remains the most commonly used material to fill cranial defects following DC

(7, 32–34). It is biocompatible and quite cost-free. Whenever available, autologous bone thus remains the favored option for filling small- to medium-size defects, as well as even the large cranial defects following DC. It is however more likely to be associated with bone flap resorption (BFR) in the latter. The BFR is a non-linear process, which can result in structural breakdown of the CP requiring reoperation and even bone flap replacement with heterologous materials.

Korhonen et al. reported BFR as a complication occurring at various degrees in up to 90% of patients undergoing autologous CP after DC, in particular in patients younger than 30 years. In any case, it has been observed that postoperative monitoring for BFR required regular clinical follow-up, assessing for mechanical stability rather than routine CT.

Independent risk factors for reoperation were shown to be younger age, shunt dependency, and bone flap fragmentation due to a fracture. Hence, an initial artificial bone substitute implant rather than an autograft could be recommended in all patients with a fragmented flap (35).

Compared with synthetic biomaterials, the use of autologous bone for CP is associated with significantly increased odds of reoperation (36). However, autologous bone does not seem to increase infection rates compared with synthetic material. BFR is the main cause for reoperation overall (35).

Some authors raised the possibility that higher rates of complication in autologous bone graft would be partly explained by bone flap conservation methods. However, a systematic review performed by Corliss et al. found no such statistical evidence (37).

PMMA

PMMA is a very common material for CP, and it can be found used as PMMA liquid or as solid PMMA customized implants. Intraoperatively, liquid PMMA takes from 10 to 20 min to be turned into a moldable viscous paste, which is then applied to the cranial defect (38). This process is an exothermic reaction from which the brain and the meninges need to be shielded. Liquid PMMA is non-absorbable, radiolucent, and inert. Additionally, it can be soaked with antibiotics, making it a good option for patients having failed multiple previous attempts at CP (38) because of SSI. It is both an effective and affordable choice for CP. The abovementioned exothermic reaction, intraoperative preparation, the relative contraindication in pregnancy, toxicity of fumes, as well as the need for artistic skills from the operators are all disadvantages.

On the other hand, solid custom-made PMMA, despite its cost, has a long-standing record, does not require to be prepared intraoperatively, does not cause any exothermic reactions, is easy to contour, is delivered sterile, as well as has a textured surface. To reduce the costs, the use of three-dimensional (3-D) patient-specific customized silicon molds is reported to be filled with less expensive liquid PMMA (39–41).

Polyetheretherketone (PEEK)

PEEK has the advantage of being inert, pliable, and mechanically sound. It requires in-house sterilization and may increase seroma formation.

Punchak et al. (42) showed a trend toward decreased postoperative complication rates of PEEK CPs compared to autologous grafts and showed a stronger trend toward lower failure rates of PEEK grafts compared to titanium grafts. The overall complication rate was shown to be lower with PEEK than with titanium group (43).

Titanium

Titanium can be manufactured as a plate, mesh, or 3-D porous implant and is available with varying stiffness and degrees of openness. Titanium is robust to resist secondary trauma while providing maximal stability of the cranial vault (44).

Titanium CP after DC is associated with better cosmetic and functional outcomes than primary autologous CP without increasing overall healthcare costs (20). Free flap coverage and soft tissue atrophy result in greater risk of titanium mesh exposure (45). The titanium mesh should be well-anchored onto the basi-temporal skull to avoid spontaneous fracture (46).

Most recently, 3-D porous titanium was implemented as a viable alternative. Despite its high cost and limited literature available, 3-D porous titanium shows promising results after a 1-year follow-up (47).

Porous Hydroxyapatite (HA)

Porous HA shows biocompatibility due to its biomimetism and the absence of host immune interactions (48–50) or systemic/local toxicity (51). Composite biomaterials such as scaffolds surface-enriched HA nanoparticle using a poly(trimethylene carbonate) (PTMC) scaffold are shown to have a positive impact on bone generation and repair (45). Bony regeneration rates were reported in two patients having undergone CP at 6 months and 2.5 years, respectively (52). It is an appropriate material for use in large and complex cranial defect reconstruction (53).

A posttraumatic fracture rate of HA prosthesis is reported but, at the same time, HA has the ability to undergo self-repair (16, 53).

A study has tried to address the retention management of infection associated with hydroxyapatite CP (52). The suggestion is that a lower biofilm formation, lower rate of colonization compared to titanium (53), targeted antimicrobial therapy, and a satisfactory area of revascularization allow optimal antibiotic delivery on-site and were all decisive in the possibility of avoiding prosthesis removal.

3-D Prosthesis

Shape is another important factor for a successful CP as an increased congruence between the patient and the implant will lead to a better outcome overall as well as improved aesthetic benefit.

In neurosurgery, 3-D printing can be used to create prosthesis and molds used to reconstruct cranial defects using CT data to obtain the dimension and shape of the repair (54, 55). The cost of equipment, lack of knowledge and training, and introduction of commercial, FDA-approved media for printing are thought to be obstacles to a widespread adoption of neurosurgical 3-D printing usage (55).

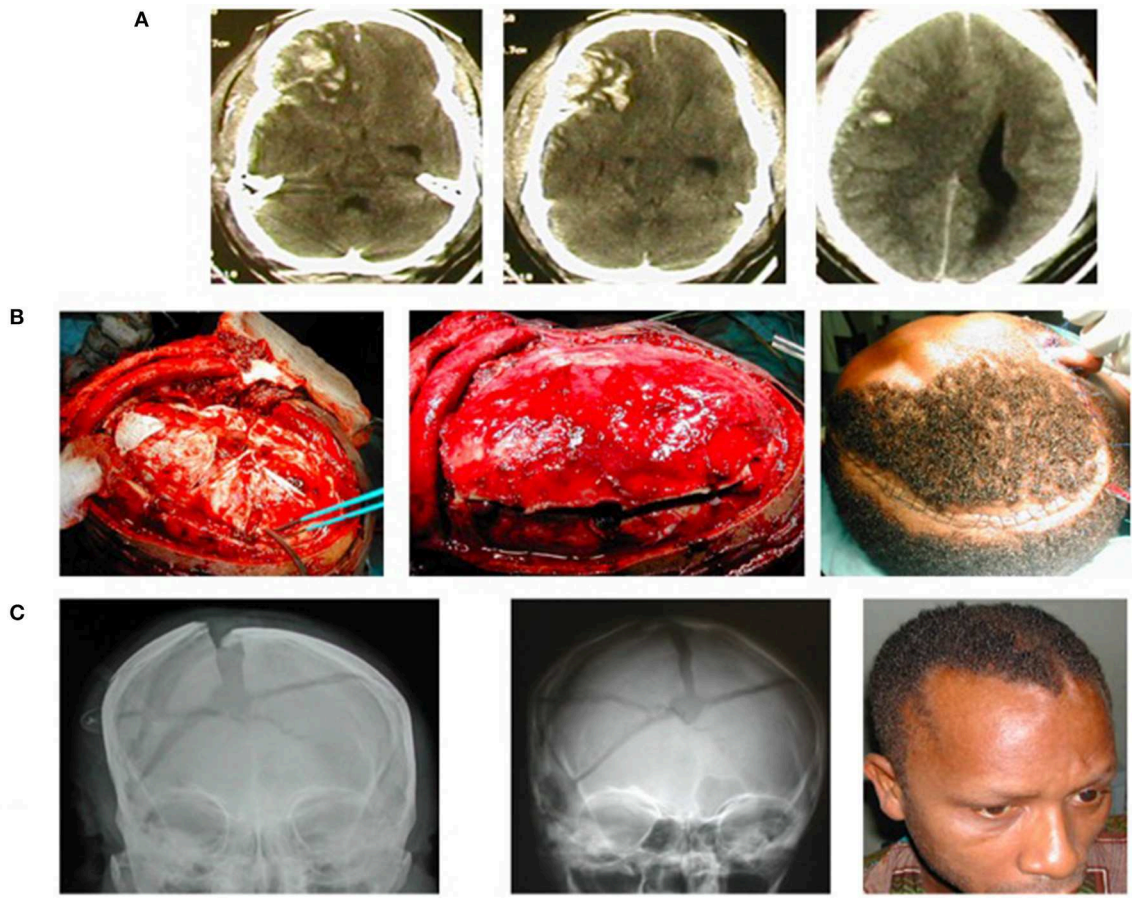

FIGURE 1 | A young man suffered severe traumatic brain injury (TBI), GCS7/15, from road trauma. **(A)** Cranial CT showed right-sided brain contusions, acute subdural hematoma, subarachnoid hemorrhage, intracerebral hematoma, and bilateral brain swelling that was worse to the right—CT Rotterdam of 6. **(B)** Intraoperative image of the hinge craniotomy, cruciate durotomy, and evacuation of the extra-axial bleed (to the left); the bone flap returned, floating *in situ* (middle); and skin closure (to the right). **(C)** Plain skull X-ray on the first postoperative day showing the elevated/floating bone flap (to the left), bone also revealed comminuted skull fracture; Plain skull X-ray (middle) and clinical picture of the patient (right) 5 weeks postop showing the bone flap spontaneously returned to the rest of the cranium following resolution of the traumatic brain swelling.

CP FOLLOWING DC IN SETTINGS WITH LIMITED RESOURCES

Until recently, the low-cost nature of the practice of neurosurgery in resource-limited regions meant that the costly protocol-driven standards of care for TBI in high-resource settings were virtually out of reach for most lower- to middle-income countries (LMICs).

However, it is now being increasingly recognized that when both clinical and radiological signs of a patient are in keeping with raised intracranial pressure (ICP) in TBI, the surgical procedure of DC should no longer be considered a last-tier treatment option. It can, and perhaps should, be performed sooner than later and most pragmatically so in these same low-resource LMICs where the other high-cost means of the non-surgical management of posttraumatic raised ICP are not available (56–59). There is therefore an increasing body of work on the use of DC in damage control surgery TBI from the developing countries.

Additionally, the surgical technique of *in situ* hinge DC (60–63) instead of the traditional DC has greatly influenced the literature of DC from the LMICs. Hinge DCs, also known as hinge craniotomies, by their nature do not as a rule require salvage CP. This would naturally be expected to be an attractive option as the surgical decompression of choice for raised ICP in the LMICs. There is thus a growing literature on the use of the hinge DC, including modifications of the originally described techniques (64–66) from these regions (**Figure 1**).

CP following DC as yet does not appear to be a major need in the LMICs. But whenever there is need to resort to the traditional DC (e.g., a forbidding massive brain swelling), then the autologous bone flap remains the overwhelming choice, and due to costs, PMMA is the second alternative.

TIMING OF CP

The appropriate timing of CP after DC in relation to complication rate and outcome has yet to be established. The

TABLE 1 | Studies evaluating timing of cranioplasty after craniectomy.

References	Study design	No. of Pts	Age (mean)	Definition of early cranioplasty	Complication rate (%)	Notes
Chun and Yi (67)	Restrospective cohort	45	49	<1 month	46.7	Early cranioplasty with significantly lower rate of complications (6.67% early, 53.3% late).
Chang et al. (68)	Restrospective cohort	212	44	<3 months	12.7	Early cranioplasty with significantly lower rate of complications (OR= 0.28, 95% CI 0.11–0.68).
Matsuno et al. (69)	Case-control	206	Range −6 months−79	NR	12.1	The mean time intervals after removal of bone flap of the infected group were longer than that of the non-infected group.
Waziri et al. (70)	Case-control	17	48	NR	47	Trend toward higher rates of post-cranioplasty hydrocephalus and longer time to cranioplasty.
Archavlis et al. (71)	Restrospective cohort	200	53	<7 weeks	9.5	Early cranioplasty may have better outcome (when no edema nor infection) but appear to increase risk of deep wound infections and osteomyelitis.
Schoekler et al. (72)	Restrospective cohort	58	46	NR	26.4	Tendency of resorption if cranioplasty performed more than 2 months after. No differences in the outcome.
Tasiou et al. (73)	Pubmed research				NR	Early cranioplasty may improve the outcome in selected cases.
Qasmi et al. (74)	Prospective cohort	30	32	<12 weeks	30	Early autologous cranioplasty offer acceptable neurological outcome.
Morton et al. (34)	Restrospective cohort	754	44	<1 month	24.6	Cranioplasty 15–30 days reduce infection, seizure, resorption, <90 days reduces hydrocephalus.
Beauchamp et al. (75)	Case-control	69	30	NR	39.1	No statistical significant difference in time to cranioplasty between those with and those without complications.
De Bonis et al. (14)	Restrospective cohort	185	All adults	<3 months	19.7	No significant difference in complication rates for early or late cranioplasty.
Gooch et al. (76)	Restrospective cohort	62	32	<1 month	33.8	OR for complications requiring reoperation was highest for patients undergoing cranioplasty 100–136 days after craniectomy.
Song et al. (77)	Restrospective cohort	43	NR	<12 weeks	NR	No effect on complication rate and global outcome by GOS.
Huang et al. (78)	Restrospective cohort	105	41.9	NR	9.5	Timing of cranioplasty is not related to outcome.
Piedra et al. (79)	Restrospective cohort (Vascular)	74	47	<10 weeks	18.9	Complication are similar for early and delayed cranioplasty.
Piedra et al. (80)	Restrospective cohort (Traumatic)	157	29.5	<12 weeks	35	Early cranioplasty does not alter the incidence of Complication.
Mukherjee et al. (17)	Retrospective cohort	144	41	<16 weeks	26.4	No difference in pre- and post-op GOS between time intervals.
Sundseth et al. (81)	Retrospective cohort (non-traumatic)	47	47.8	NR	26.4	Timing of cranioplasty is not related to the risk of infection
Kim et al. (82)	Retrospective cohort	85	50.3	<1 month	7.05	No statistical difference in infection rate between the 2 groups
Coulter et al. (83)	Restrospective cohort	166	39	NR	40.4	Timing of cranioplasty did not appear to be predictive of outcome.
Tsang et al. (28)	Restrospective cohort	NR	46.3	<3 months	16.7	Timing of cranioplasty had no significant association with complications.
Krause-Titz et al. (84)	Restrospective cohort	248		NR	18.5	Timing of cranioplasty had no significant influence on complications.
Schuss et al. (85)	Restrospective cohort	280	46	<2 months	16.4	Early cranioplasty with significantly higher rates of complications (25.9% early vs. 14.2% late).
Thavarajah et al. (86)	Restrospective cohort	82	NR	NR	11	Cranioplasty between 0 and 6 months had the greatest rate of infection.

Early cranioplasty is not uniform among the various studies. Adapted from Piedra et al. (79).

concept itself of early CP remains ill-defined and refers to time intervals varying from as little as 4 weeks up to as long as 12 weeks (**Table 1**).

Timing varies according to three pre-CP scenarios encountered, setting the earliest time at which a CP can be performed.

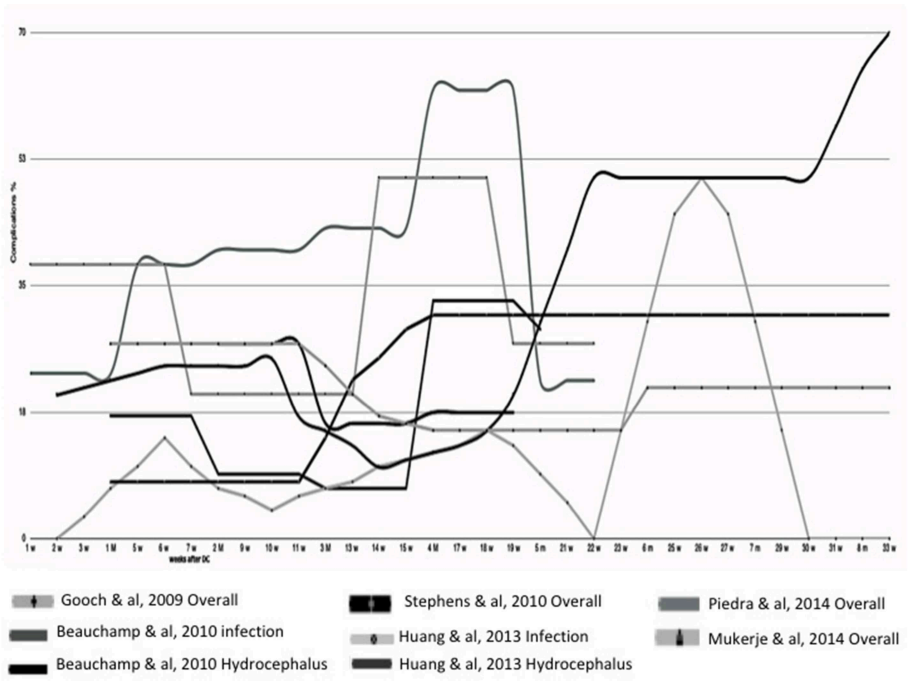

FIGURE 2 | Timing of Cranioplasty. In this graph are compared different clinical courses after cranioplasty analyzed from different papers, where the timing of onset of complication is well-reported. In this partial analysis of literature data, a higher rate of complication is suggested when cranioplasty has been performed between the third and fifth month.

Type 1: The brain is depressed with a significant sinking of the post-DC flap due to a posttraumatic brain atrophy or overdrainage of a ventriculoperitoneal shunt (VPS). Thus, a pre-CP long-lasting CSF diversion should be avoided.

Type 2: The post-craniectomy scalp flap is at the same level as the margins of the cranial vault. The brain should be in the most physiological condition thus at a low risk of observing the development of HC and/or postoperative blood collections.

Type 3: The post-craniectomy scalp flap is over the cranial vault margin due to brain swelling and/or HC/VM. This could well be the worst scenario due to the difficulty of diagnosis and treatment.

Infection was reported to be the highest risk within 14 days of craniectomy, HC within 90 days, and seizure risk after 90 days. Hence, some advocate for an ultra-early CP taking place between 15 and 30 days that would minimize infection, seizure, and autologous flap resorption risks.

In a retrospective cohort study (71), the functional outcome was found to be better for CP performed at the <7 weeks and at 7–12 weeks group compared with the >12 weeks group. Nevertheless, the authors stressed an earlier time to CP should be set as soon as brain edema had normalized so as to have higher chances of a better neurologic outcome and not apparently increased infection rate. At the same time, CP performed at <7 weeks was associated with a significant increase in infection rates when comorbidities, such as diabetes, thromboembolism, and colonization with multidrug resistant (MDR) pathogens, were present (87). Thus, both clinical status and infective status are strong determinants of the outcome of an early CP (<7 weeks) and are of paramount importance in establishing the timing of an early CP.

Conclusions regarding early CP vary widely among different studies (75, 76, 88). Some authors attribute a lower rate of complications to an early CP (67–69, 71, 73, 74), others describe a lower risk of hydrocephalus (34, 70), while no improvement in outcome following early CP was also found (72, 78). Moreover, no impact of timing on outcome (17, 83) or complications (3, 14, 28, 77, 79–82, 84) have been reported. Only two authors (85, 86) associated an early CP with poor outcome, in particular, the highest rate of infection between 0 and 6 months (86). An analysis of literature data suggests a higher rate of complication when CP has been performed between the third and fifth month (**Figure 2**).

Last reported systematic review and meta-analysis (3) suggested that early CP may lead to even greater improvements. Nevertheless, despite a growing consensus that earlier is better, no more than low-level evidence from retrospective, poorly matched cohort studies (Class IIb, Level C) has been published on this subject.

CONCLUSION

Despite its therapeutic and cosmetic advantages, CP following DC is not reported to correlate strongly with improved neurologic rehabilitation and outcome.

Different surgical approaches can be used to reduce the surgical complications that may arise at any point of the clinical course among which bifrontal CP is a strong independent risk factor.

Autologous bone is the most commonly used material despite its association with BFR and higher rate of implant failure requiring removal.

A consensus has yet to be reached with regard to the best heterologous material for CP. Porous prostheses may offer promising results despite higher costs.

Standards of care for DC are not applicable in LMICs due to high costs, and thus autologous bone grafts are favored.

Regarding HC, the optimal timing for shunting is yet to be firmly defined. A one-step surgery with CP and CSF shunting and a two-step surgery with or without external CSF drainage are reported as alternatives of management. Finally, CSF shunting without a timely CP should be avoided.

While waiting for results of an ongoing randomized controlled trial (RCT) on early vs. late CP promoted by NIHR Global Health Research Group on Neurotrauma, the timing of reconstructive CP should rather be based on an objective case-by-case assessment of the neurological status of each patient, resolution of brain swelling, and complications associated with large calvarial defects rather than arbitrary time windows (73) and should be performed as soon as brain swelling resolves on CT scan, provided that the patient is not in an infectious state (89).

The authors are aware that the results of future studies may dictate updating many of the recommendations on several aspects of CP after DC contained in this review.

AUTHOR CONTRIBUTIONS

CI, AK, AA, and L-GR: writing manuscript. CI and AA: analysis of literature. CI and AA: collecting cases. AK and KF: supervision of manuscript.

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Conflict of Interest: CI is a consulent for post market surveillance for Finceramica S.p.A.

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