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Comparison of Decompressive Craniectomy and Maximal Medical Management with Barbiturates in Severe Traumatic Brain Injury Patients with Refractory ICP: A Randomized Controlled Study

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Abstract

Context: Traumatic brain injury is the major cause of death and disability worldwide. Management of severe traumatic brain injury still remains elusive, some prefer surgical intervention while others advocate medical treatment. *Objective:* To compare the effect of decompressive craniectomy (DC) and maximal medical management with barbiturates in management of severe Traumatic Brain Injury (sTBI) patients with refractory Intracranial pressure (ICP). *Settings and Design*: 57 patients of severe traumatic brain injury admitted from September 2013 to august 2015 were evaluated based on inclusion and exclusion criteria and subjected to ICP monitoring. *Materials and Methods*: Patients with ICP refractory to conventional medical management (n=37) were randomized to decompressive craniectomy (n=23) or maximal medical management with addition of barbiturates (n=14). The primary outcome was functional status on Extended Glasgow Outcome Scale (GOS-E) at 7 days and 3 months. Secondary outcome measures were assessment of ICP control and days of hospitalization. *Statistical Analysis used:* Chi-square test and Student's *t*-test were used for data analysis. Logistic regression analysis was employed to assess the effect of multiple variables in the outcome. *Results:* In decompressive craniectomy group (23), the mean ICP was reduced from 27.81 to 14.06 mmHg after surgery. Eight patientsin this group were alive at 3 months, among which 7 (30.43%) patients achieved good GOS-E of ≥ 4. Among 14 patients who underwent medical management with barbiturates the mean ICP reduced from 27.82 to 20.41 mmHg after therapy. In this group, one patient was alive (GOS-E 3) at 3 months. None of the patients in barbiturate group achieved good GOS-E (score ≥ 4) at 3 months. *Conclusion:* ICP monitoring of sTBI patients helps in early identification of patients whose ICP becomes refractory to conventional treatment methods. Decompressive craniectomy provides better outcome in terms of survival and achievement of good outcome as compared to maximal medical management with barbiturates

Keywords: Intracranial Pressure; Severe Traumatic Brain Injury; Decompressive Craniectomy; Barbiturate.

Introduction

Severe traumatic brain injury is the major cause of death in trauma patients [1]. With current available best practices, only about 1/3rd of patients are able to live independently in long term and the rest are severely disabled or dead[2]. Guidelines for management of sTBI recommend ICP monitoring in sTBI patients and to maintain ICP less than 20 mm Hg [3], above which treatment has to be started. CT scan cannot reliably predict ICP [4]. The only way to reliably determine Cerebral Perfusion Pressure (CPP) is continuous ICP monitoring and blood pressure monitoring [5,6].

Recent guidelines recommend decompressive craniectomy (DC) as salvage therapy for medically refractory ICP in sTBI patients [7,8], but there is a lack of class – I evidence comparing DC with medical management for treatment of sTBI. Many reviews have been written describing the relevant data for [9,10] and against [11,12] DC for sTBI with overwhelming conclusion that RCTs are required to resolve these disputes [7].

Our study was designed to randomize the patients of severe traumatic brain injury with refractory raised ICP into two arms: Surgical Managementgroup - decompressive craniectomy (SM) or maximal Medical

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Management group (MM) and to compare their effect on outcome of patients with sTBI.

Clinical Material and Methods

The study was undertaken at Department of Neurosurgery, King George's Medical University, Lucknow, UP, India from September 2013 – August 2015 by identifying and recruitings TBI patients based on the inclusion and exclusion criteria after taking institutional ethical committee approval. Ethical clearance was obtained from the institutional ethics committee of KGMU. An informed written consent was taken from the first degree relative of the patient after explaining details of the study.

The inclusion criteria were -Patients with closed sTBI between 16 to 60 years of age, GCS 8 or less and CT showing no surgically evacuable lesion. Exclusion criteria were GCS-3, coagulation disorder, previous craniectomy, spinal cord injury, pregnant female and who were not willing to take part in the study.

A total of 57 patients were enrolled in the study and were subjected to ICP monitoring by placing ventricular catheter /sub arachnoid bolt (Shenzhen goldway/G30). First line treatment (head end elevation, endotracheal intubation or tracheostomy, hydration, oxygenation, maintain ABG and electrolytes, analgesics) was started in all the patients to keep the ICP below 20 mm Hg. Antibiotics, antiepileptics and supportive care were given. Second line of treatment (sedation, paralysis, CSF drainage, osmotherapy, diuretics) was started if ICP did not respond to first line measures. All the patients were kept in the intensive care unit (ICU) with close monitoring of vital parameters and blood coagulation profile by a team consisting of neurosurgeons, neurophysicians, and critical care experts. Serum sodium, potassium, calcium, and magnesium were checked daily and necessary corrections were done. Acid base imbalance was monitored and corrected. 20 out of 57 patients responded to first and second line treatment for ICP control. These patients were not the part of further study.

We defined refractory elevation in ICP as a spontaneous (not stimulated) increase in ICP above 20 mm Hg for more than 15 minutes (continuously or intermittently) within a 1-hour period, despite optimized second - line interventions. 37 out of 57 patients hadrefractory elevation in ICP and were randomized into two-treatment arm SM or MM.14 patients were randomized to receive MMand 23 patients were randomized to receive SM. Randomization was done by computer generated random binary numbers and to maintain concealment of allocation, a computer operator's (a nonmedical staff) help was taken.

Patients in MM group continued with first and second line treatment along with barbiturate (thiopental sodium). Loading dose 3mg/kg and then 10 to 20 mg/kg infusion over 1 hour followed by 3-5 mg/kg maintenance dose were given. The dose was maintained according to the blood pressure and ICP control readings. In this group decompressive craniectomy was performed only at the clinician's discretion if the patient subsequently deteriorates (e.g. prolonged and unacceptably high ICP > 40 mmHg with compromised CPP).

Surgical Procedure- Decompressive Craniectomy

For unilateral decompressive craniectomy that was done in our patients, the patient was placed supine with a small rolled towel underneath the ipsilateral shoulder and the head turned towards the contralateral side.Once the site was prepped and draped, a large question mark incision was made starting at the level of the zygoma and curving posteriorly above the ear, over the parieto-occipital region, and then superiorly and anteriorly, approximately 2 cm lateral to the midline, and stopping just behind the hairline. The posterior extent of the incision was more than 15 cm behind the keyhole to allow for an adequate craniectomy flap. Care was taken to protect the superficial temporal artery to preserve blood supply to the skin flap. The incision extended through the subcutaneous tissue, including the temporalis muscle, down to the cranium. The resultant myocutaneous flap was then reflected anteriorly and fixed with scalp hooks. The temporalis dissection was carried down to the zygoma to adequately expose the temporal bone and maximize the temporal decompression.

A hemicraniectomy flap with an anteroposterior dimension of at least 15 cm and extended down as far as possible toward the floor of the temporal fossa were made. Preferences for the location and number of burr holes varied, but typically six to seven burr holes were made: one at the keyhole, one more inferiorly in the temporal bone, posterior to the sphenoid bone, three superoposteriorly in the parietal bone and one in the frontal bone. Dura was separated from bone with Penfield's No. 3 dissector. Gigli's guide introduced with care in extradural space. Gigli's wire saw was used for craniectomy. The flap

was then turned. After hemostasis is obtained, the temporal extent of the craniectomy was examined and, if necessary, expanded down to the floor of the middle cranial fossa by using a rongeur. Before proceeding with the dural opening, it was important to achieve hemostasis with the bone and epidural space with bone wax and dural tack-up stitches, respectively. The dural opening was made leaving safe margin from bone edges. Temporal lobectomy was performed if required on the basis of surgeon's intraoperative impression of persistently bulged and non-relaxed brain. Augmentation of dura was done by using pericranium. Closure was done in layers. Subgaleal drain was placed for 48 hours. Surgery was performed by the first author in supervision of senior surgeons (other authors).

ICP was monitored continuously and readings were recorded at hourly interval. ICP was monitored for 72 hours in all the patients. Patients with refractory ICP were randomized and treatment continued as for the randomized group. If ICP was below 20 mmHg or responding to first and second line of treatment monitoring was discontinued after 72 hours. Barbiturate infusion was continued for patients in MM group if ICP was responding and infusion rate slowly tapered according to the ICP readings and then stopped. ICP monitoring was continued for 24 hours post operatively in patients who underwent decompressive craniectomy.

Baseline demographic and clinical parameters consisting of mode of injury, GCS, pupillary status, vital parameters and initial CT grade with the use of the Marshall criteria. Hourly ICP and mean arterial pressure measurements were recorded. Therapeutic interventions and surgical complications were noted. The primary outcome variable was functional status at 7 days and 3 months measured using Glasgow Outcome Scale Extended (GOS-E). GOS-E of 4 or more was taken as good outcome. Secondary outcome measures were assessment of ICP control and days of hospitalization.

The data was analyzed using the Statistical Package for Social Sciences version 15 (SPSS Inc.); Chi-square test and Student's *t*-test were used for data analysis. Logistic regression analysis was employed to assess the effect of multiple variables in the outcome. The confidence level of the study was kept at 95%, hence a *P* value less than 0.05 indicated a statistically significant association.

Results

The baseline characteristics of both groups were comparable with respect to age, sex, mode of injury, best motor response at admission, GCS score, pupillary reaction and CT Marshall grade [13] as given in Table 1. The mean ICP at onset in both MM group (27.8mm Hg) and SM group (27.8mm Hg) were comparable.

Table 1: Demographic details of patients with refractory ICP

Variables		SM group(n=23)	MM group(n=14)	p value
Mean Age (years)		31.8±13.14	29.9±7.31	t=0.484 P=0.631
Sex	Male	15 (65.2%)	13 (92.8%)	X^2=3.61
	Female	8 (34.7%)	1(7.1%)	P=0.057
Admitting GCS	4-5	10(43.5%)	10(71.4%)	X^2=2.74
	6-8	13(56.5%)	4(28.6%)	P=0.098
Mode of Injury	RTA	19 (82.6%)	13 (92.8%)	X^2=0.782
	FFH	4 (17.4%)	1(7.1%)	P=0.377
Pupil reactivity	Abnormal reaction	7 (30.4%)	8 (57.1%)	X^2=2.58
	Normal reaction	16 (69.6%)	6 (42.9%)	P=0.109
Marshall CT class	Diffuse injury 2-3	9 (39.13%)	12 (85.71%)	X^2=7.69
	Diffuse injury 4	14 (60.86%)	2 (14.28%)	P=0.006
Mean intracranial pressure at onset in mm Hg		27.8±9.4	27.8±20.3	t=0.002 P=0.998
Mean ICP post intervention in mm Hg		14.0±6.8	20.4±14.4	t=1.826 P=0.076
ICP >30mmHg at onset		12 (52.1%)	8 (57.14%)	X^2=0.087 P=0.769

Primary Outcome

After 7 days, 12 patients were dead (GOS-1), 4 were in vegetative state (GOS-2) and 7 were in lower disability group (GOS-3) in SM group whereas 8 patients were dead (GOS-1) and 6 were in vegetative state (GOS-2) in MM group [Table 2]. None of the patients in both the groups had favorable outcome at 7 days.

After 3 months among 23 patients who were in SM group, 8 patients were alive at 3 months in which 1 patient was in GOS-E 3, 4 patients were in GOS-E 4, two patients were in GOS-5 and 1patient had GOS-E 6. In MM group only one patient was surviving at 3 months with GOS 3. GOS-E of 4 or more considered as favorable outcome. So at 3 months, 7 patients in SM group had favorable outcome. None of the patients in MM group had favorable outcome [p=0.022. X^2=5.26 (df=1)] at 3 months [Table 2].

Secondary Outcome

After surgical and medical intervention in respective groups, the mean ICP was 14 mm Hg in SM group and it was 20.4 mm Hg in MM group (p=0.076.t= 1.826) Mean duration of hospital stay was 9.3 days (range 4 - 25 days) in SM group and 8 days (range 2- 16 days) in MM group as depicted in Table 2.

Complications

Patients in SM group had complications like wound infection (n=3), subgaleal collection (n= 6), Acute renal failure (ARF)(n=3), pneumonia (n=8), hydrocephalus (n=2,) and infarction (n=1). Patients in MM group had suffered complication like pneumonia (n=3), ARF, hydrocephalus, infarction and hypotension (n=1, each). [Table 3].

Table 2: Primary and secondary outcome at 7 days and 3 months

Outcome	SM group (n= 23)	MM group (n=14)	p value
Extended Glasgow outcome scale at 7 days			
1 dead	12/23 (52.17%)	8/14 (57.14%)	-
2 vegetative state	4/23 (17.39%)	6/14 (42.85%)	-
3 Lower severe disability	7/23 (30.43%)	-	-
4 upper severe disability	-	-	-
Extended Glasgow outcome scale at 3 months	-	-	-
1 dead	15/23 (65.21%)	13/14 (92.85%)	-
2 vegetative state	-	-	-
3 lower severe disability	1/23 (4.34%)	1/14 (7.14%)	-
4 upper severe disability	4/23 (17.39%)	-	-
5 lower moderate disability	2/23 (8.69%)	-	-
6 upper moderate disability	1/23 (4.34%)	-	-
7 lower good recovery	-	-	-
8 upper good recovery	-	-	-
No of patients alive at 3months	8/23(34.7%)	1/14(7.1%)	-
favorable scores ≥ 4 at 7 days	0	0	-
favorable scores ≥ 4 at 3 months	7/23 (30.43%)	0	X^2=5.26(df=1) P=0.022
Mean ICP post intervention (mm Hg)	14.06±6.8	20.4±14.4	t= 1.514 p=0.138
Duration of hospital stay (days)	9.3±5.89	8±2.69	t= 0.829 p=0.413

Table 3: Medical and surgical complications in both groups

Complications	SM group	MM group
Wound infection	3	0
Subgaleal collection	6	0
CSF leak	0	0
Acute renal failure	3	1
Pneumonia	8	3
Hydrocephalus	2	1
Infarct	1	1
Hypotension	0	1

Table 4: Predictors of death after decompressive craniectomy

Variables	SM group (n=23)	No. of deaths associated with each variable	'p' value for death rate (Fischer exact test)
CT characteristics			
>5 mm mid line shift(Marshall class -4)	14/23	11/14 (78.6%)	p=0.176
Marshall class – 3	9/23	4/9 (33.3%)	1.000
Admission GCS score			
4 to 5	10/23	10/10 (100%)	p<0.001
6 to 8	13/23	5/13 (38.5%)	0.737
Admission motor score on Glasgow coma scale			
2 to 3	10/23	10/10 (100%)	p<0.001
4 to 6	13/23	5/13(38.4%)	0.737
Abnormal pupillary response to light			
No pupillary reaction	7/23	6/7 (85.7%)	p=0.007
Pupillary reaction present	16/23	9/16 (56.2%)	-
ICP at randomization			
>30 mm Hg	12/23	9/12 (75%)	p=0.282
20-30 mm Hg	11/23	6/11 (54.5%)	0.325

Predictors of Mortality

We analyzed the potential predictors of mortality after decompressive craniectomy [Table 4]. There was 78.5% mortality in patients with class-4 Marshall CT as compared to 33.3% in patients with Marshall Class 3 CT finding (p=0.176). There was 100% mortality in patients who were operated with admission GCS of ≤ 5 and motor score of ≤ 3 compared to 38.4% in patients with GCS of ≥ 6 and motor score ≥ 4 (p=<0.001). Patients with abnormal pupillary reaction had 85.7% mortality compared to 56.2% in patients with normal pupillary reaction (p=0.007). There was 75% mortality in patients who had ICP more than 30 mm Hg compared to 54.5% patients with ICP between 20 to 30 mm Hg (p = 0.282).

Discussion

Traumatic brain injury (TBI) is the leading cause of death and long-term disability in the first four decades of life and will surpass many diseases as the major cause of death and disability by the year 2020. In our study, around 90% of patients were under 40 years of age (mean age of 29 years) and 90% of the study population was of male gender. Around 90% of our study population had sustained injury in a road traffic accident. Similar age and gender distribution among traumatic brain injury patients has been found in most of the research studies, these include studies by Aarabi et al. (2006) [14], Cooper at al. (2011) [15], Carney et al .(2012) [16], and Chestnut et al. (2012) [17] etc. Motor vehicular accident has been found to be the most common mode of injury in all these studies as is observed in our study.

ICP Monitoring

The 'Guidelines for the Management of Severe Traumatic Brain Injury 4th Edition' published in 2016 recommend for monitoring Intra cranial pressure of all patients with severe traumatic brain injury (GCS 4-8) with abnormal CT (level 2 evidence),

though there is insufficient level 1 data to support ICP monitoring in severe traumatic brain injury patients [7]. An abnormal CT scan of head is the one that reveals hematomas, contusions, swelling, herniation or compressed basal cisterns. Although ICP monitoring is recommended in all sTBI patients, it is not universally practiced.

ICP data can be used to predict outcome and worsening intracranial pathology, calculate and manage CPP, allow therapeutic CSF drainage with ventricular ICP monitoring and restrict potentially deleterious ICP reduction therapies. ICP monitoring can be the first indicator for worsening intracranial pathology and surgical mass lesions. In a study by Servadei et al on 110 consecutive patients of traumatic sub arachnoid hemorrhage, ICP monitoring was the first indicator of evolving lesions in sTBI group, four out of five patients received operative treatment [18]. In our study, 57 patients were selected for ICP monitoring, out of which 20 patients did not required to be subjected to aggressive and risky measures to lower ICP blindly as their ICP measurements did not reflect need for such treatment modalities (Responders to first / second line treatment) whereas 37 had persistently raised ICP (refractory ICP) requiring furtheraggressive treatment. Thus ICP monitoring guided in our study for identifying responders to standard medical treatment and delineating refractory ones needing further aggressive line of treatment. Jennett et al. [19], Bower & Marshall [20], Colohan et al. [21] and Ghajar et al. [22] have supported ICP monitoring based management of traumatic brain injury for producing more favourable outcomes. ICP data can be useful in predicting prognosis and in guiding therapy in victims of severe traumatic brain injury.

The treatment of refractory raised ICP is challenging. The options include decompressive craniectomy or addition of drugs like barbiturates to medical management.

Role of Decompressive Craniectomy

In our study, there were 23 patients randomized to undergo decompressive craniectomy. The mean ICP in this group was 27.8 mm Hg before intervention which was reduced to a mean value of 14.06 mm Hg. following decompressive craniectomy. Similar reductions in ICP post decompressive craniectomy has been reported in other studies like Howard et al. [23] (2008; from 35.0±13.5 to 14.6±8.7 mm Hg; $p<0.005$), Timofeev et al. [24](2008; from 36.4 to 12.6 mm Hg), Skoglund et al.[25] (2006; from 29.2±3.5 to 11.1±6.0 mm Hg), Whitfield et al. [26] (2001; 50.2±16.6% to 15.7±10.7%).

Taylor et al., in their study of 27 pediatric TBI patients randomized the patients to bitemporal craniectomy plus medical management (n=13) or medical management alone (n=14). Bitemporal craniectomy was associated with a mean ICP reduction of 9.0 mmHg, which was 5.3mmHg more than medical management alone. Overall, 54% of the decompression group versus only 14% of the control group reached a favorable GOS score after 6 month [27].

The Decompressive Craniectomy (DECRA) trial was the first prospective multicenter RCT comparing bifrontal craniectomy (n=73) with standard non-surgical care (n=82) for patients with refractory intracranial hypertension [15]. Despite fewer days in the intensive care unit ($p<0.001$) and improvements in ICP ($p<0.001$), the DC group had more unfavorable outcomes (odds ratio 2.21; $p=0.02$) and worse GOS-E scores (odds ratio 1.84; $p=0.03$). There was no significant difference in mortality (19% in the DC group vs. 18% with medical management) or length of hospital stay (28 vs. 37 days, respectively; $p=0.82$). In the present study, patients undergone surgical management had more favourable outcome (GOS E scores) than those undergone maximal medical management ($p=0.022$) at 3 months of follow up. SM group had better ICP reductions and favourable outcome as compared to MM group in our study that disagrees with the results of DECRA trial.

In our study, the predictors of poor outcome (death) were more than 5 mm. mid line shift on CT scans, admission GCS scores of 4-5, low values of motor scores on Glasgow coma scale (2-3),CPP <60 mm Hg and mean ICP at admission of more than 30 mm Hg. Similar poor outcome predictors were noted in a retrospective study by Lemcke et al. [28],Pfenninger et al. [29], Andrews et al. [30] (asymmetric pupil reactivity, older age, greater degree of midline shift, initial GCS score of 8 or less, hypotension, clotting disorders or obliteration of basal cisterns). However, the statistical significance of association of these variables with poor outcome after decompressive craniectomy could not be established in our study except for admission GCS less than 5, motor score less than 3 and abnormal papillary reaction ($p=0.007$).

Role of Maximal Medical Management with Barbiturates

Some of the strongest support for the efficacy of lowering intracranial hypertension in improving outcomes comes from a prospective randomized trial of high-dose barbiturate therapy for refractory intracranial hypertension reported by Eisenberg et al. in 1988 [31]. They randomized 73 patients with

refractory ICP elevation to either high-dose pentobarbital ('barbiturate coma') or continuation of aggressive treatment without barbiturates. Patients in whom ICP responded had a 1-month mortality rate of 8%, whereas 83% of those who did not respond were dead at that point. In our study, 14 patients were randomized to MM group. Only one patient was alive at 3 months in this group. The mean ICP in this group at the time of randomization was 27.8 mm Hg and was reduced to mean value of 20.4 mm Hg post intervention.

Decompressive Craniectomy v/s Maximal Medical Management with Barbiturates

Gower et al. [32] (1988) compared pentobarbital coma (n=24) and sub temporal decompression (n=10) in severe TBI patients treated for medically refractory ICP. Authors observed mortality rate of 82% in patients who received barbiturates coma. The mortality rate was 40% in patients who underwent decompression. Authors stated that decompressive craniectomy could be used as a salvageable procedure in patients with refractory ICP elevation. The major deficiency of this study was lack of statistical analysis.

We observed that both surgery and barbiturates were effective in reducing the raised ICP. Despite reduction in ICP more than 50% of the patients died post intervention within 7 days in both the groups. At 3 months SM group patients had better outcome compared to patients who received maximal medical management with barbiturates in the form of survival (8/23,34.9%vs 1/14,7.1%) and favorable GOS-E (7/23,30.4%vs none/14). This states supremacy of decompressive craniectomy over maximal medical management in refractory ICP patients of sTBI.

The fact that high intracranial pressure after traumatic brain injury is associated with poor outcome is now well established. It is still not clear whether reversing intra cranial hypertension translates to improved outcome or high values of this parameter after sustaining severe head injury is just a marker of disease severity.

Conclusions

ICP monitoring is to be done in all traumatic head injury patient with the CT feature of raised ICP. Decompressive craniectomy and maximal medical treatment with barbiturates are feasible options for reduction of refractory ICP. Our study showed better survival at 3 months and better response in patients who underwent decompressive craniectomy. Favorable outcome at 3 months was found to be far better in patient's undergone decompressive craniectomy than barbiturate treated ones thus tilting scales in favor of surgical procedure and establishing its superiority.

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Conflict of Interest

The authors certify that they have no conflict of interest

Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional ethics committee.

Informed Consent

Informed consent was obtained from all individual participants included in the study.

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