Decompressive Craniectomy for the Treatment of Severe Diffuse Traumatic Brain Injury: A Randomized Controlled Trial

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Abstract

Background  Severe traumatic brain injury (TBI) is one of the leading public health problems across the world. TBI is associated with high economic costs to the healthcare system specially in developing countries. Decompressive craniectomy is a procedure in which an area of the skull is removed to increase the volume of intracranial compartment. There are various techniques of decompressive craniectomy used that include subtemporal and circular decompression, and unilateral or bilateral frontotemporo-parietal decompression.

Objective  The aim of this study was to compare the outcome of decompressive craniectomy for the management of severe TBI versus conservative management alone at the Department of Neurosurgery, Abbasi Shaheed Hospital, Karachi, Pakistan.

Methods  The study (randomized controlled trial) was conducted from February 1, 2014, till June 30, 2017.

Results  A total of 136 patients were included after following the inclusion criteria. They were randomly assigned to two groups, making it 68 patients in each study group. There were 89 males and 47 females. All the patients received standard care recommended by the Brain Trauma Foundation. The mortality rate observed at 6 months in decompressive craniectomy was 22.05%, while among conservative management group, it was 45.58%. Difference in mortality of both groups at 6 months was significant. Total 61.76% (42) of patients from decompressive craniectomy group had a favorable outcome (Glasgow outcome scale: 4–5) at 6 months. While among conservative management group, total 35.29% (24) had a favorable outcome (Glasgow outcome scale: 4–5). Difference in Glasgow outcome scale at 6 months of both groups was significant.

Conclusion  In conclusion, decompressive craniectomy is simple, safe, and better than conservative management alone.
Introduction and Historical Background

Severe traumatic brain injury (TBI) is one of the leading public health problems across the world. TBI is associated with high economic costs to the healthcare system, especially in the developing countries. TBI is recognized as a major cause of death in young populations (age < 45), with a current global mortality of 39%, and not far behind is high intracranial pressure (ICP) as a cause of death and morbidity after TBI. The use of surgical decompression in the form of decompressive craniectomy (DC) has increased substantially in the past 20 years. Some research has reported that DC has certain advantages over conservative approaches. It lowers ICP, improves cerebral perfusion, decreases secondary brain damage; therefore, it shortens duration of mechanical ventilation, intensive care unit (ICU), and hospital stay, mortality, and improves functional recovery.

The concept behind this treatment is to achieve significant cranial volume expansion. The reduction in ICP after DC has been statistically significant in a study by Olivecrona et al. The indications and timing of the DC surgery are still discussed in the literature and vary across centers in Pakistan and throughout the world. There are many factors that can influence the outcome and age is certainly one of the factors that should be taken into account when making the decision to perform a DC. There is some agreement that the prognosis is better at a younger age and that early DC, within 24 hours after onset, is better than late.

DC is a procedure in which an area of skull is removed to increase the volume of intracranial compartment. There are various techniques of DC used that include subtemporal and circular decompression, unilateral or bilateral frontotemporo-parietal decompression. Recently DC has created ethical puzzle because of the large number of disabled survivors. However, it is increasingly clear that DC, combined with modern neurointensive care, offers the potential to save life with acceptable functional outcome. Recently two famous randomized trials were performed by Cooper et al. and Hutchinson et al. In the article by Hutchinson et al, DC was related to better scores of Glasgow outcome scale—extended (GOS-E) but similar unfavorable outcomes compared with medical care, while Cooper et al reported that DC was linked with poor GOS-E scores and significantly higher unfavorable outcomes. In view of the inconsistencies, more large-scale studies were needed to explain the result of DC on functional outcomes.

As there is discrepancy between results offered by the two available treatment options, and since there is a lack of data available within Pakistan, we undertook this study to compare the GOS between DC and conservative management for severe diffuse TBI.

Objective

The objective of the study is to compare the outcome of DC for management of severe TBI versus conservative management alone at Department of Neurosurgery, Abbasi Shaheed Hospital, Karachi.

Hypothesis

DC has better outcome than conservative management alone for the treatment of severe TBI.

Operational Definition

Mortality: The frequency of deaths in 6 months out of the patients included in the study.

Favorable Score: GOS of 4 or 5 after 1 month is considered favorable score.

Unfavorable Score: GOS of 1 or 2 or 3 after 1 month is considered unfavorable score.

Duration of Mechanical Ventilation: Total number of days when the patient is on mechanical ventilation.

Duration of ICU stay: Total number of days when the patient is admitted in ICU.

Duration of hospital stay: Total number of days when the patient is admitted in the hospital.

Materials and Methods

Study Design
Randomized controlled trial.

Setting
This study was conducted in Department of Neurosurgery in Abbasi Shaheed Hospital (ASH), a tertiary care teaching hospital of Karachi Medical and Dental College (KMDC), Karachi.
Table 2  Glasgow coma scale

<table>
<thead>
<tr>
<th>Eye opening response</th>
<th>Verbal response</th>
<th>Motor response</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 = Spontaneous</td>
<td>5 = Oriented</td>
<td>6 = Obey command</td>
</tr>
<tr>
<td>3 = To verbal stimuli</td>
<td>4 = Confused</td>
<td>5 = Localizes pain</td>
</tr>
<tr>
<td>2 = To pain</td>
<td>3 = Inappropriate words</td>
<td>4 = Withdraws from pain</td>
</tr>
<tr>
<td>1 = None</td>
<td>2 = Incoherent</td>
<td>3 = Flexion to pain or decorticate</td>
</tr>
</tbody>
</table>

Duration of Study
The study was conducted from February 1, 2014, till June 30, 2017.

Sampling Technique
Probability sampling using random permuted blocks.

Sample Size
Sample size is calculated using EPI info software. Mortality in craniectomy is 29.3%, and in conservative group, mortality is 58.3% \(\beta = 80\%), \alpha = 5\% then the estimate sample size will be at least \(\eta = 34\) in each group and total sample size will be at least \(\eta = 68\). To give the current study power, we decided to double the sample size with \(\eta = 68\) in each group and total number of patients as \(\eta = 136\).

Inclusion Criteria
All patients who were admitted from the emergency room and their attendant or next of kin gave written consent to be the part of study and were having the following characteristics:

1. Age between 15 and 60 years
2. Diffuse TBI
3. Glasgow coma scale (GCS) more than or equal to 3 to less than 8 (Table 2)
4. Injury within 12 hours at randomization
5. ICP more than 20 for more than 15 minutes despite medical management.

Exclusion Criteria
Following groups of patients were excluded from this study:

1. Mass lesion: extradural hematoma/subdural hematoma/contusion
2. Penetrating head injury
3. Associated spinal injury
4. Unreactive pupils more than 4 mm, and GCS = 3
5. Coagulopathy
6. Cardiac arrest
7. Diagnosed cases of chronic liver, kidney disease, diabetes, and patients with carcinoma.

Research Scheme
Prior approval from Ethical and Scientific Review Committee of the hospital and medical college was obtained. The study was conducted as part of dissertation for Neurosurgical Training Fellowship under College of Physician and Surgeons Pakistan (CPSP). Ethical approval was granted by KMDC and ASH ethical committee, synopsis was approved by research evaluation unit of CPSP, and dissertation was subsequently approved.

All the patients with severe diffuse TBI presented in emergency room were considered for the trial and selected on the basis of inclusion and exclusion criteria. Soon after the resuscitation in the emergency room, all patients were admitted to ICU, intubated, and ventilated. Intraparenchymal ICP monitoring was performed. ICP and mean arterial pressure were recorded every hour for first 6 hours before randomization. The risks and benefits of the procedure were explained to the attendants or next of kin and after obtaining their written consent to take part in the study, the patients were included in the study. The patients were randomized in ICU by using sealed envelope technique and assigned to group “A” (decompressive craniectomy) and group “B” (conservative management). The surgeon enclosed the two treatment options on separate papers in opaque envelopes. An equal number of envelopes were available in ICU. The surgeon mixed the envelopes and open one to reveal randomization arm.

Both groups of patients received standard care recommended by the Brain Trauma Foundation. Patients were sedated, analgesed, and ventilated. They were nursed head up. Early phase of ICU care included close monitoring of a multitude of systemic physiological variables, including hemodynamic parameters, pulse oximetry, temperature, hemoglobin level, blood glucose, electrolyte panel, and fluid intake and output. Targets for physiological parameters were ICP not to exceed 20, cerebral perfusion pressure more than 60 mm Hg (central venous pressure: 6–10), oxygen saturation more than 97%, arterial CO2 4.5–5.0 kPa, temperature less than 37°C, and blood sugar 4 to 7 mmol/L. Mannitol and hypertonic saline were administered to patients when required. Inotropes were used to increase mean arterial pressure to maintain cerebral perfusion pressure when necessary. Cerebral perfusion pressure was calculated by subtracting ICP from the mean arterial blood pressure.

Late phase of ICU care involved weaning and liberation from the life support, including ventilation, and mobilization in preparation for transfer to ward setting. Many had to undergo tracheostomy to ensure the patency of airway with low GCS and hence liberty from ventilation. Patients with swallowing problems required the placement of a gastrostomy tube to facilitate long-term tube feeding, hence minimizing the risk of aspiration.

For patients included in group A, DC was performed within 4 hours of inclusion in the study. The surgical
technique described by Huang and Wen was used. The operation comprised unilateral DC with a single frontotemporoparietal bone flap or a large bilateral frontotemporoparietal craniectomy with bilateral durotomy. The hemisphere was inspected for hematoma or bleeding and hemostasis was obtained after evacuation of hematoma if present. Anyone found to have intracranial hematoma intraoperatively was excluded from the study. The bone flap was stored in an abdominal pouch created surgically in the subcutaneous space in the anterior abdominal wall. The bone flap was replaced within 60 days of surgery when the brain swelling subsided. All procedures were performed by the same group of consultant neurosurgeons. Anyone who underwent decompressive craniectomy as a lifesaving procedure after randomization was excluded from the study.

Data Collection
Basic demographic data recorded in ICU with clinical scenario from medical records. The early data comprised of mechanism of injury, GCS at scene, GCS in emergency room, computed tomography (CT) scan findings classified as per Marshall criteria. Patients were followed throughout their hospitalization and variables like duration of mechanical ventilation, duration of ICU stay, duration of hospital stay, mortality, morbidity, and GOS at 1 month were recorded.

Surgical complications and nonsurgical complications were recorded separately. Follow-up was continued for more than 6 months and data for both groups were collected and completed at the time of follow-up in the outpatient clinic.

Statistical Analysis
Statistical packages for social sciences version 19 (SPSS 19) were used to analyze data. Mean ± standard deviation was calculated for quantitative variables, that is, age of the patient, duration of hospital stay, duration of ICU stay, and duration of mechanical ventilation in days. Frequency and percentages were calculated for qualitative variables, that is, gender and mortality and favorable outcome. We minimized confounding factors by stratification of data performed with age, gender, duration of hospital stay, duration of ICU stay, and duration of mechanical ventilation through chi-squared test. p-Value of 0.05 or lower was considered significant. Chi-squared test was applied to mortality and favorable scores in both groups taken p-value of 0.05 or lower as significant.

Results
It took us more than 3 years to complete the trial. More than 5,000 patients with TBI were evaluated for qualification in the study, and 170 patients were enrolled for this study (►Fig. 1).

Fig. 1 Flowchart explaining screening, selection, inclusion, and exclusion of patients.
Majority of reason for exclusion from the trial was nonavailability of consent, or refusal of consent from family members, and the second common reason for exclusion from study population was the presence of an intracerebral hematoma. Out of 89 patients who were initially included in the study and were randomly assigned to the conservatively managed group, 21 (23.5%) patients were excluded from the study population as they either were transferred to different hospital, consent was withdrawn from the family, or nine (10.1%) patients had delayed DC as a salvage procedure. Out of 81 patients who were initially included in study and were randomly assigned to the DC group, 13 (16%) patients had to be removed from the study as either they were transferred to different institution or family withdrew the consent. One hundred and thirty-six patients were included after following the inclusion criteria. They were randomly assigned to both groups, making it 68 patients in each study group. Majority of the patients (96; 70.58%) sustained head injury due to Road Traffic accident, with second most common cause being assault (29; 21.32%). The remaining 11 patients had miscellaneous mode of injury listed in Table 3.

Out of 136 patients of our study population, there were 89 (65.44%) males and 47 (34.55%) females (Table 2). Age was normally distributed as shown by the p-value that was calculated through independent t-test and it was 0.682 that was not significant. Gender proportion was normally distributed as shown by the p-value that was calculated through Pearson chi-squared test and it was 0.840 that was not significant.

**Outcome**

Outcome of both groups was measured by duration of mechanical ventilation, duration of ICU stay, duration of hospital stay, mortality, and GOS at 6 months. DC group has shown better outcome when we compared mean duration of mechanical ventilation (11.76 days), standard deviation (5.17), standard error (0.62), and 95% confidence interval (CI) (10.5–12.9), while mean duration of mechanical ventilation for conservative management group was 15.14 days, standard deviation was 3.87, standard error was 0.46, and 95% CI was 14.22 to 16.05. Mean duration of ICU stay for DC was 13.82 days, standard deviation was 3.67, standard error was 0.44, 95% CI was 12.94 to 14.69, while mean of conservative management group was 18.88 days, standard deviation was 4.77, standard error was 0.57, 95% CI was 1.74 to 20.01, with range 9 days to 29 days. Mean duration of hospital stay for DC was 35.11 days, standard deviation was 12.25, standard error was 1.48, 95% CI was 32.19 to 38.02, while mean of conservative management group was 40.2 days, standard deviation was 11.15, standard error was 1.35, 95% CI was 37.55 to 42.85 with range 19 to 61 days (Table 2).

Patients who had decompressive craniectomy had a favorable outcome (GOS: 4–5) at 6 months than the conservative management group. Favorable outcome transpired in 63.6% of patients (42) who underwent DC; odds ratio is 2.96 for a favorable outcome in craniectomy group, 95% CI, 0.47 to 5.94; p-value 0.0023. Total 15 patients (22.05%) from DC and 31 (45.58%) patients died within 6 months. Odds ratio is 2.96 for survival after DC versus conservatively managed group, 95% CI, 0.40 to 6.24; p-value 0.0043.

**Complications**

Three most common complications were same in both the groups. Ventilator-associated pneumonia was the most common complication in both the groups with 23.52% (16) in DC and 30.88% (21) in conservative management group, followed by electrolyte imbalance and urinary tract infection (Table 5). The spectrum of complications was wider in DC group, with eight patients having wound infection, three patients having CSF leak, three patients having CNS infection, two patients having significant evolution of contusion requiring surgery, and two patients having abdominal wound infection and both had bone flap resorption.

**Discussion**

In our study population with severe diffuse TBI and medically incorrigible ICP, results show that DC decreased ICP, the duration of mechanical ventilation, duration of ICU stay, duration of hospital stay, with significantly low mortality and favorable GOS at 6 months. These findings are in contrast with Cooper et al7 and harmonize with most nonrandomized studies of DC19,20 The results are in accordance with our study hypothesis. We have noticed that the DC group showed early positive clinical signs in the ICU. It is safe to believe that DC is an operation to save lives, a procedure that can help with management of uncontrollable ICP and minimize secondary brain damages as previously expected.

### Table 3 Mode of injury with number of patients and percentage in each category

<table>
<thead>
<tr>
<th>Main category, n (%)</th>
<th>RTA, 96 (70.58%)</th>
<th>Assault, 29 (21.32%)</th>
<th>Industrial injury, 5 (3.6%)</th>
<th>Fall from height, 4 (2.9%)</th>
<th>Hit by animal, 2 (1.4%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subgroup, n (%)</td>
<td>Motorcycle, 65 (67.7%)</td>
<td>Blunt injury with stick, 17 (58.62%)</td>
<td>Brick/stone, 7 (24.13%)</td>
<td>Pushed from roof, 5 (17.24%)</td>
<td>Hit by a cow, 1 (50%)</td>
</tr>
<tr>
<td></td>
<td>Car, 20 (20.83%)</td>
<td>Brick/stone, 7 (24.13%)</td>
<td>Hit by a horse, 1 (50%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pedestrian hit by MV, 11 (11.45%)</td>
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</tr>
</tbody>
</table>

Abbreviations: MV, motor vehicle; RTA, road traffic accident.

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In published literature, patients with moderate-to-severe TBI had favorable outcome ranging from 30% to more than 70% if they had DC, and our findings are similar with 61.76% of favorable outcome and 38.23% had unfavorable outcome that includes 22.05% mortality.

Important to note that even in the subgroup with unfavorable outcomes, DC has increased survivals, 11 out of 26 versus 13 out of 44 in conservatively managed individuals. We believe that DC helped switched the results from unfavorable outcome to a favorable outcome. Our finding states that early surgery results in better outcome that is similar as reported by others. Unilateral DC is favored procedure as opposed to bilateral decompression as it has been proven in past that the bilateral approach has more complications.

Another indispensable finding of our study was that all of the patients with presenting GCS of 7 and 8 survived after DC and showed favorable outcome. We noticed that low GCS with age above 50 was linked with poor outcome in both of the study groups. As in many other procedures, patient selection can improve outcome in severe TBI after DC.

It is important to note that some factors play significant role as a determinant in outcome of TBI; most notables are delay in surgery from TBI, age of patient, presenting GCS, and initial CT scan findings that can predict the outcome of these patients as documented in some studies. DC and cranioplasty are not without complications, and some of them may be catastrophic. Among them contusions, acute subdural hematoma, extradural hematoma, and hydrocephalus can be fatal.

Although we encountered variety of complications of DC yet the complications were statistically similar to previous studies and most of the common complications had similar percentage in both the study groups.

We believe that there is a need for a trial with longer follow-up as literature suggests the outcome of these patients can further improve with time, as published by Meier et al which states that approximately 25% of the patients who had an unfavorable outcome at 6 months improved to favorable outcome after 18 months.

### Limitations of Study

There are limitations in this study that should be mentioned. First this is a single-center study. Second, although patients

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**Table 4** Details of patients with outcome in both groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group A (craniotomy) n = 68</th>
<th>Group B (medical management) n = 68</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>44 (49.4)</td>
<td>45 (50.6)</td>
<td>0.84a</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>24 (51.1)</td>
<td>23 (48.9)</td>
<td></td>
</tr>
<tr>
<td>Age Mean ± SD</td>
<td>34.3 ± 14.1</td>
<td>34.5 ± 13</td>
<td>0.68b</td>
</tr>
<tr>
<td>Location of injury</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right, n (%)</td>
<td>29 (47.5)</td>
<td>32 (52.4)</td>
<td>0.85a</td>
</tr>
<tr>
<td>Left, n (%)</td>
<td>34 (51.5)</td>
<td>32 (49.5)</td>
<td></td>
</tr>
<tr>
<td>Bilateral, n (%)</td>
<td>5 (55.5)</td>
<td>4 (54.5)</td>
<td></td>
</tr>
<tr>
<td>GCS score at baseline</td>
<td></td>
<td></td>
<td>0.97a</td>
</tr>
<tr>
<td>4–5, n (%)</td>
<td>24 (48.9)</td>
<td>25 (51.1)</td>
<td></td>
</tr>
<tr>
<td>6–7, n (%)</td>
<td>29 (50)</td>
<td>29 (50)</td>
<td></td>
</tr>
<tr>
<td>8, n (%)</td>
<td>15 (51.7)</td>
<td>14 (48.3)</td>
<td></td>
</tr>
<tr>
<td>GOS score at 6 months</td>
<td></td>
<td></td>
<td>0.003a</td>
</tr>
<tr>
<td>≥ 4 n (%)</td>
<td>42 (63.6)</td>
<td>24 (36.4)</td>
<td></td>
</tr>
<tr>
<td>≤ 3 n (%)</td>
<td>26 (38.2)</td>
<td>44 (61.8)</td>
<td></td>
</tr>
<tr>
<td>Mean duration of mechanical ventilation (hours) Mean ± SD</td>
<td>11.76 ± 5.17</td>
<td>15.14 ± 3.87</td>
<td>&lt; 0.0001c</td>
</tr>
<tr>
<td>Mean days of ICU stay</td>
<td>Mean ± SD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>13.82 ± 3.67</td>
<td>18.88 ± 4.77</td>
<td>&lt; 0.0001c</td>
</tr>
<tr>
<td>Mean days of hospital stay</td>
<td>Mean ± SD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>35.11 ± 12.25</td>
<td>40.2 ± 11.15</td>
<td>&lt; 0.0001c</td>
</tr>
<tr>
<td>Mortality at 6 months, n (%)</td>
<td>15 (22.05%)</td>
<td>31 (45.58%)</td>
<td>&lt; 0.0001a</td>
</tr>
</tbody>
</table>

Abbreviations: GCS, Glasgow coma scale; GOS, Glasgow outcome scale; ICU, intensive care unit; SD, standard deviation.

*aPearson chi-square test.
*bStudent t-test.
*cMann–Whitney U test.

*p < 0.05 is significant.
were followed for longer duration, the data was only collected till 6 months. Third, there was no blinding in this study and everyone involved in the care of these patients including the investigators assessing the outcome were familiar with the study.

Additionally, the topic of floating or hinged bone flaps as a potential alternative to DC for TBI is one more field of conflict which this study failed to address. Consequent cranioplasty can be avoided with a Floating or hinged bone flaps that have shown promising results in controlling at most moderate swelling after TBI.

34,35 This is crucial to consider in low- and medium-income countries.

**Conclusion**

In conclusion, DC is simple, safe, and better than conservative management alone. The present results strongly support further large, multicenter clinical trials to evaluate the difference of the effects between DC and other means of management in acute post-traumatic brain swelling after severe TBI.

**Conflict of Interest**

None declared.

**References**


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**Table 5 Complications in both the groups of study population**

<table>
<thead>
<tr>
<th>Complications of decompressive craniectomy (A), n (%)</th>
<th>Complications of conservative management (B), n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ventilator associated pneumonia, 15 (22.05%)</td>
<td>Ventilator-associated pneumonia, 21 (30.88%)</td>
</tr>
<tr>
<td>Electrolyte imbalance, 13 (19.11%)</td>
<td>Electrolyte imbalance, 18 (26.47%)</td>
</tr>
<tr>
<td>Urinary tract infection, 9 (13.23%)</td>
<td>Urinary tract infection, 13 (19.11%)</td>
</tr>
<tr>
<td>Wound infection, 8 (11.7%)</td>
<td>Seizures, 9 (13.23%)</td>
</tr>
<tr>
<td>Seizures, 7 (10.29%)</td>
<td>Deep vein thrombosis/pulmonary embolism, 4 (5.88%)</td>
</tr>
<tr>
<td>Hydrocephalus, 6 (8.82%)</td>
<td>Meningitis/ventriculitis, 2 (2.94%)</td>
</tr>
<tr>
<td>Sepsis, 4 (5.88%)</td>
<td></td>
</tr>
<tr>
<td>Deep vein thrombosis/pulmonary embolism, 3 (4.41%)</td>
<td></td>
</tr>
<tr>
<td>Cerebrospinal fluid leak, 3 (4.41%)</td>
<td></td>
</tr>
<tr>
<td>Meningitis/subdural empyema/abscess, 3 (4.41%)</td>
<td></td>
</tr>
<tr>
<td>Acute subdural hematoma requiring surgery, 2 (2.94%)</td>
<td></td>
</tr>
<tr>
<td>Contusions requiring surgery, 2 (2.94%)</td>
<td></td>
</tr>
<tr>
<td>Bone flap resorption, 2 (2.94%)</td>
<td></td>
</tr>
<tr>
<td>Abdominal wound infection, 2 (2.94%)</td>
<td></td>
</tr>
<tr>
<td>Subdural hygroma requiring surgery, 1 (1.47%)</td>
<td></td>
</tr>
<tr>
<td>Chronic subdural hematoma requiring surgery, 1 (1.47%)</td>
<td></td>
</tr>
</tbody>
</table>

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factors and a discussion about some novel prognostic parameters. J Pak Med Assoc 2013;63(01):38–49