ORIGINAL ARTICLE

Severe Traumatic Brain Injury: Outcome in Patients with Diffuse Axonal Injury Managed Conservatively in Hospital Sultanah Aminah, Johor Bahru – An Observational Study

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SUMMARY

Patients with isolated severe head injury with diffuse axonal injury and without any surgical lesion may be treated safely without cerebral resuscitation and intracranial pressure (ICP) monitoring. Seventy two patients were divided into three groups of patients receiving treatment based on ICP-CPP-targeted, or conservative methods either with or without ventilation support. The characteristics of these three groups were compared based on age, gender, Glasgow Coma Scale (GCS), pupillary reaction to light, computerized tomography scanning according to the Marshall classification, duration of intensive care unit (ICU) stays, Glasgow Outcome Score (GOS) and possible complications. There were higher risk of mortality *($p < 0.001$)*, worse GCS improvement upon discharge *($p < 0.001$)* and longer ICU stays ($p = 0.016$) in ICP group compared to Intubation group. There were no significant statistical differences of GOS at 3rd and 6th months between all three groups.

KEY WORDS:

Severe traumatic brain injury, Diffuse axonal injury, Intracranial pressure monitoring, Outcome

INTRODUCTION

Severe traumatic brain injury (TBI) has been one of the major causes of death in Malaysia. It is a leading cause of death in the younger generations which include children and adult younger than 45 years old [1]. The leading cause of traumatic brain injuries is motor vehicle accidents and head injury features a common cause of death in road traffic accidents (RTA). It probably accounts for three quarter of the morbidity and mortality rates in RTA in the country. In Malaysia, the incidence of road traffic accident is one of the highest in the world with about 22 deaths per 100,000 populations[2]. There are about six thousands two hundreds deaths per annum recorded since year 2003, while almost ten thousands victims sustained severe disabilities. The figure of mortality has not taking account of those admitted with severe TBI and eventually died in the hospital. While the rate of TBI-related hospitalization is declining in developed countries like United States due to better injury prevention[3], there are increasing trends of such needs in developing countries like Malaysia. This has been a big financial burden to the country.

Hospitalizations of those sustained severe injuries involve the utilization of beds in intensive care unit. In Malaysia, a total of 276 ICU beds available in all government hospitals[4]. Hospitalization of severe injured patients occupied about 25 beds per admission per day. This is about ten percent of all ICU beds available. There are only seven general hospitals and three university hospitals in Malaysia with neurosurgical services. With such limited numbers of ICU beds and limited numbers of neurosurgical intensive care units in Malaysia, certainly there will be shortage of facilities needed to cater for a larger number of severe traumatic brain injured patients. The presence guidelines given by Brain Trauma Foundation for the management of patient with severe traumatic brain injury (GCS $\leq$ 8) with an abnormal CT brain findings on admission or a normal CT scan findings on admission but fulfilling 2 out 3 clinical criteria, which include age above 40 years old, abnormal motor response and episodes of hypotension (SBP < 90 mmHg) is to ICP-monitored and cerebral protected, based on cerebral perfusion pressure (CPP) and ICP guide[5]. The recommendations given by Brain Trauma Foundation in the management of severe traumatic brain injury patients cannot be implemented for all patients with such limitation. Additional criteria are set for the selection of TBI patients who will be benefited most from the intensive neurosurgical treatment.

In this study, we aim to report the outcome of three groups of severe traumatic brain injury with diffuse axonal injury and non-surgical lesion, based on ICP-CPP (Group A); Without ICP but ventilation support (Group B) and without ICP and ventilation support (Group C) as initial treatment modalities. The division of patients into these three groups was based on the decision of the neurosurgeon on call in consideration of resources available. The limited resources include ventilated beds in neurosurgical ICU and ICP monitoring device (spiegelberg catheters) which influence the decision made during admission. This was done to determine the disadvantages of alternative treatments given with such limitations.

MATERIALS AND METHODS

This was a prospective observational study of severe traumatic brain injury patients admitted with diffuse axonal injury without surgical lesion to Neurosurgical Intensive Care Unit, Hospital Sultanah Aminah, Johor Bahru. The study was conducted between 1st December 2006 and 31st May 2008 with a total of seventy two patients included in the study. The patients' recruitment periods were from 1st December

This article was accepted: 23 September 2009
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2006 to 30th November 2007. The follow-up periods were at the 3rd month and 6th month from the date of discharge of the recruited patients, which ended on 31st May 2008.

Severe head injured patient was defined as a patient who was admitted with Glasgow Coma Score (GCS) of $\leq$ 8 cumulative points after adequate resuscitation. The inclusion criteria were as follows: a) GCS of 8 or below on admission; b) Blunt non-operative head injury (diffuse axonal injury). The exclusion criteria were as follows: a) Polytrauma which causing unstable hemodynamic status, requiring immediate non head surgical intervention and post operative ventilation support; b) Severe underlying medical disorders such as major organ failure, endocrinological or hematological disorder, suspected drug or alcohol intoxication, mentally subnormal, or history of chronic epilepsy before the event of head trauma; c) Patients who on arrival had unilateral or bilateral fixed and dilated pupils believed to be due to ongoing herniation, clinically showing absence of brain stem reflexes, with no improvement after resuscitation or failed resuscitation upon admission; d) Patients who had a known history of hemiparesis, or had any other condition that lowered the patient's functional status score; e) Patients with surgically treatable traumatic brain lesions.

All the selected patients were admitted via emergency department. The referred patients were resuscitated, stabilized and intubated at referral hospital prior to transfer. Directly admitted patients were resuscitated, stabilized and intubated at emergency department. Subsequently all patients were sent for Computed tomography (CT) scan brain from the emergency department except those patients referred from district hospital with CT scan facility, such as Hospital Sultan Ismail and Hospital Muar. All patients were reviewed by neurosurgical team and other respective departments at emergency department before transferring to the Neurosurgical Intensive Care Unit.

Intracranial brain injuries were classified according to Marshall Classification. Checklists were given to all patients admitted to Neurosurgical Intensive Care Unit (NICU). Patients who fulfilled the selection criteria will have additional form placed in their folder and recorded daily. Upon discharged from the ward to either district hospital or home, GOS form was placed inside the follow-up folder and was filled up during clinic follow-up. Patients who defaulted the follow-up were called via phone for his or her progress.

Group A

Neurosurgical consultant on call was consulted and decision was made by him if patients were to be subjected for ICP catheter placement and ICP-CPP-targeted management. This procedure was usually performed in the operating theatre unless all operation rooms were occupied at that particular moment. In this condition, the procedure was performed at bedside under aseptic technique. Spiegelberg double lumen intra ventricular ICP catheter was inserted at the end of the operation and connected to the Spiegelberg Compliance-Monitor.

Group B

In the situation when spigelberg catheter used for ICP was not available, the neurosurgeon may then decide to ventilate the patients in neurosurgical ICU, with either heavily sedated or with light sedation. The decision of weaning of sedation usually based on the findings noted in subsequent repeated CT scan. In those who developed deterioration and with the availability of ICP device, they will be subjected with ICP monitoring.

Group C

In situation when ventilated bed was not available, the neurosurgeon may then decide to intubate the patients with oxygen connection. In condition when respiratory failure developed or if clinical condition of the patients deteriorate, and with the availability of ventilation support, they were connected to ventilator.

Data entry and analysis was done using Statistical Package for Social Sciences (SPSS) version 12.0.1 Means and standard deviations were calculated for continuous variables, and frequency and percentages for categorical variables. Independent t-test was used to compare mean differences with the level of statistical significance set at 0.05. The prognostic factors of Diffuse Axonal Injury in severe traumatic brain injury were done using Proportional Hazards Models.

RESULTS

Seventy two patients with severe traumatic brain injury with diffuse axonal injury (DAI) were treated in NICU, Hospital Sultanah Aminah, Johor Bahru between 1st December 2006 and 30th November 2007 after exclusion criteria were applied.

A. Demography

Demographically as shown in Table I, there were no significant differences in all three groups in term of age distribution, gender, ethnic group, admission systolic blood pressure (SBP) and pulse rate, episode of hypotension and pupillary reactivity. However there were statistically significant differences in GCS on admission, rapid eye movement, pupillary equality ($p < 0.05$) (Table II). Patients in group A and B were admitted with poorer GCS which were between 3 and 5 with 26.7% in group A and 37.5% in group B. Most patients in group C were in a better GCS on admission, which were between 6 and 8 (95.1%). In addition, patients in group A had more percentage of absent of rapid eye movement on admission and unilateral dilatation of pupils compared to group B and C. Most group C patients who were not intubated and ICP monitored had near normal motor responses with either localizing to pain or normal flexion. On the other hand, almost equal distribution of patients with normal and abnormal motor responses in group A and B. However, the differences were not statistically significant. In term of Marshall grading of CT scan on admission, there were also uneven distribution of cases in severity. There was only Marshall Grade I and II in group C. (Table III). There were also 19% without cerebral edema seen among patients in group C, while all patients in group A and B presented with cerebral edema seen in CT scan, and this was statistically significant ($p = 0.033$). There were also significantly higher numbers of patients with subarachnoid hemorrhage and base of skull fractures in group A and B compared to group C with $p = 0.008$ and $p = 0.029$

respectively. In term of associated cervical injury, there were statistically higher in group B in comparison to group C ($p < 0.001$).

The uneven distribution of cases based on Marshall Grades in each groups were analyzed and mean grade were calculated (Table IV). The patients in group A were obviously had poorer Marshall Grade with mean grade of 2.40, compared to group C with mean grade of 1.78. The difference was statistically significant ($p < 0.001$).

B. Treatment

1) Group A

There were only fifteen (20.8%) patients have been treated with standard ICP-CPP guided cerebral resuscitation (Table V). Ten patients were with CT scan of Marshall Grade II, four patients of Marshall Grade III and only one with Marshall Grade IV (Table III). Eventually, ten (66.7%) of them required tracheostomy (Table V). Inotropic and mannitol usage were the highest in this treatment group with a total of thirteen (86.7%) and six (40.0%) patients respectively (Table V). The higher usage of inotropic drug in group A compared to both group B and C were statistically significant, $p = 0.001$ and $p < 0.001$ respectively (Table VI). There were also high number of complications, with six (37.5%) patients had pneumonia, three with septicemia and two with urinary tract infection (UTI) (Table VII). There was a single patient complicated with cardiac event, two with acute renal failure, one patient each with disseminated intravenous coagulopathy (DIVC) and diabetes insipidus (DI).

A total of 375 recordings of ICP measurement of all 15 patients treated with ICP-CPP guided management (Table IX). The mean ICP was 15.96mmHg (SD 8.24). 81.6% of readings were recorded below 20mmHg, 13.3% between 20-25mmHg, 3.5% between 25-30mmHg and only 6 readings (1.6%) recorded above 30mmHg.

2) Group B

A total number of sixteen patients were treated with ventilation support with the availability of ventilators in neurosurgical ICU without ICP monitoring (Table V). Two patients were heavily sedated for cerebral resuscitation. They were sedated with either IV Morphine and / or Midazolam or combination of IV Propofol and Fentanyl infusion. There were seven patients ventilated without sedation. Twelve (75%) of them were subjected for tracheostomy (Table V). A total of six (37.5%) patients required usage of inotrope, while only one was given iv mannitol therapy (Table V). A high number of patients complicated with pneumonia, with a total of six (50%), but only one with septicemia and two with UTI (Table VII). Pulmonary edema was diagnosed in one patient and two were complicated with disseminated intravenous coagulopathy (DIVC) (Table VII).

3) Group C

Of seventy two patients admitted for diffuse axonal injuries, without any surgical lesion, forty one (56.2%) were just treated with intubation for airway protection, and given oxygen via oxyvent device with continuous oxygen saturation monitoring (Table V). Of all patients in the intubation group, fifteen of them were given light sedation with either IV Midazolam alone or with combination of Morphine and / or Midazolam (Table V). There were only nineteen (46.3%) patients in this category subjected for tracheostomy (Table V). There were only three patients who required inotropic infusions to maintain mean artery pressure (MAP). Seven (17.1%) patients were given mannitol therapy (Table V). A total of eleven patients (26.8%) complicated with pneumonia, two with septicemia and three with urinary tract infection (UTI) (Table VII). There was no significant higher risk of pneumonia in any of the groups (Table VIII). Two patients complicated with upper gastrointestinal (GI) bleed, and one with pulmonary edema (Table VII).

C. Outcome

Eleven (11) patients died during hospitalization (15.3%) (Table X). Out of remaining 61 patients, only 49 patients (80.3%) were follow-up during first three months (with three deaths) and 45 out of 58 patients (77.6%) were follow-up during subsequent 3 months (with no death detected). There were only sixty one (84.7%) patients were discharged from hospital, whereby twenty nine (40.3%) with good outcome (GOS 4 and 5) while the remaining thirty two (44.4%) patients were with either severe disability or persistent vegetative state (Table X). For the first three months follow-up, only forty six (75.4%) patients turned up for consultations. Three absentees were subsequently made known dead at district hospital via phone call and the remaining twelve patients (19.7%) were un-contactable. From those who been reviewed, seven (14.3%) were either moderate or severely disabled and thirty nine (79.6%) patients with good recovery (Table X). On the next six months follow-up, there were only forty five (76.3%) patients came for follow-up (Table X). There was left only with one patient with severe disability, while the rest were improved with either moderate or good recovery (Table X).

1) Group A

There were seven (46.7%) mortalities (Table X). Upon first three months follow-up, there were only one mortality was detected, six patients (75%) with good outcomes and one (12.5%) with severe disability (Table X). At six months follow-up, there was 100% recovery to good Glasgow Outcome Score (GOS) (excluding one defaulter).

2) Group B

In ventilation group, there were only three deaths (18.8%) each suffers from Marshall Grade II, III and IV. For the first three months follow-up, another two patients succumbed at district hospitals, three patients having severe disabilities and 6 patients (54.6%) with good outcome. Two patients were missing from follow-up. At six months follow-up, there were almost 89% patients with good recovery and only 11% with poor GOS (Table X).

3) Group C

There was a single death in this group. There was no known death at three and six months follow-up. Group C had the biggest number of defaulters during the follow-up. The reason for this may be a high number of discharged patients with good GOS in this group. In term of morbidity, there was 100% of recovery at 6 months excluding those who had defaulted the follow-up (Table X). The outcome of patients in this group was better than those in group A, and was statistically significant ($p < 0.001$) (Table X). However, there

Table I: Demographic of severe traumatic brain injury with diffuse axonal injury

Demographic	Group A	Group B	Group C	Total	P value
Age(years) Mean(SD)	35.3(18.20)	37.5(11.01)	32.5(14.65)	34.2(14.71)	0.499
Age Group					
<20 years	5(33.3)	0	10(24.4)	15(20.8)	
21-30 years	2(13.3)	4(25.0)	11(28.8)	17(23.6)	
31-40 years	2(13.3)	6(37.5)	6(14.6)	14(19.4)	
41-50 years	2(13.3)	3(18.8)	7(17.1)	12(16.7)	
51-60 years	2(13.3)	3(18.8)	5(12.2)	10(13.9)	
>60 years	2(13.3)	0	2 (4.9)	4 (5.6)	
Gender					
Male	12(80.0)	14(87.5)	35(85.4)	61(84.7)	0.838
Female	3(20.0)	2(12.5)	6(14.6)	11(15.3)	
Ethnic Group					
Malay	9(60.0)	8(50.0)	25(61.0)	42(58.3)	0.941
Chinese	3(20.0)	6(37.5)	5(12.2)	14(19.4)	
Indian	3(20.0)	2(12.5)	10(24.4)	15(20.8)	
Others	0	0	1 (2.4)	1 (1.4)	

Table II: Clinical characteristic of severe traumatic brain injury with diffuse axonal injury

Clinical	Group A	Group B	Group C	Total	P value
SBP on admission [mean(SD)]	140.2(47.2)	141.2(16.1)	134.2(21.7)	137.0(27.7)	0.613
Episode of hypotension					
Present	2(13.3)	1(6.3)	1 (2.4)	4 (5.6)	0.295
Absent	13(86.7)	15(93.8)	40(97.6)	68(94.4)	
Pulse Rate on admission [mean(SD)]	78.1(20.0)	79.4(20.0)	77.6(16.1)	78.1(17.6)	0.943
GCS on admission					
3-5	4(26.7)	6(37.5)	2 (4.9)	12(16.7)	0.005
6-8	11(73.3)	10(62.5)	39(95.1)	60(83.3)	
Motor response on admission					
1-3	7(46.7)	7(43.8)	8(19.5)	22(30.6)	0.064
4-5	8(53.3)	9(56.3)	33(80.5)	50(69.4)	
Rapid Eye Movement					
Present	3(20.0)	9(56.3)	27(34.1)	39(54.2)	0.008
Absent	12(80.0)	7(43.8)	14(34.1)	33(45.8)	
Pupillary Equality					
Equal	5(33.3)	11(68.8)	31(75.6)	47(65.3)	0.011
Unilateral dilatation	9(60.0)	5(31.3)	9(23.0)	23(31.9)	
Bilateral dilatation	1 (6.7)	0	1 (1.4)	2 (2.8)	0.530
Pupil Reactivity					
Reactive	8(53.3)	10(62.5)	31(75.6)	49(68.1)	0.255
Non-reactive	7(46.7)	6(37.5)	10(24.4)	23(31.9)	

were no statistically significant difference in term of outcomes at three and six months follow-up between all three groups (Table X). In term of survival after six months follow-up, patients in group A had a higher risk of mortality compared to patients in group C, and was statistically significant ($p < 0.001$).

D. Comparison of other variables in all three treatment modalities

1) Repeat CT scan

Fifty two (72.2%) patients had at least one repeat CT scan done (Table XI). Twenty nine (55.8%) of them were treated with just intubations, while fourteen (26.9%) with ventilation support and remaining nine (17.3%) were treated with ICP-CPP-targeted management. There were no statistically significant differences in term of the need for a repeat CT scan (Table XII) and the mean numbers of repeat CT scan (Table XIII) in all three groups.

2) Length of hospitalization

The mean length of hospitalization in group A and B were longer than in group C (Table XIV). However, the differences were not significant statistically.

3) Length of ICU stays

The mean length of intensive care unit (ICU) stay was longer in group A compared to group B and C (Table XV). The mean day of ICU stay in Group A was 8.20 days compared with mean of only 4.79 days in group C, and was statistically significant ($p = 0.016$).

4) Improvement in GCS

A comparison of difference between the Glasgow coma score (GCS) upon admission and discharge were made. A mean of small improvement of 0.47 score in group A compared to a bigger mean of improvement of 5.12 scores in group C. This findings showed a marked improvement in GCS of patients in group C compared to group A, and was statistically significant ($p < 0.001$).

Table III: Imaging characteristic of severe traumatic brain injury with diffuse axonal injury

Imaging	Group A [n(%)]	Group B [n(%)]	Group C [n(%)]	Total [n(%)]	P value
Computed Tomography Marshall's Grade on admission					
Grade I	0	1 (6.3)	9(22.0)	10(13.9)	<0.001
Grade II	10(66.7)	13(81.3)	32(78.0)	55(76.4)	
Grade III	4(26.7)	1 (6.3)	0	5 (6.9)	
Grade IV	1 (6.7)	1 (6.3)	0	2 (2.8)	
Cerebral Edema					
Present	15(100.0)	16(100.0)	33(80.5)	64(88.9)	0.033
Absent	0	0	8(19.5)	8(11.1)	
Grey-white Junction hemorrhage					
Present	11(73.3)	10(62.5)	24(58.5)	45(62.5)	0.609
Absent	4(26.7)	6(37.5)	17(41.5)	27(37.5)	
Deep Hemorrhage					
Present	8(53.3)	5(31.3)	20(48.8)	33(45.8)	0.407
Absent	7(46.7)	11(68.8)	21(51.2)	39(54.2)	
Subarachnoid hemorrhage					
Present	13(86.7)	10(62.5)	17(41.5)	40(55.6)	0.008
Absent	2(13.3)	6(37.5)	24(58.5)	32(44.4)	
Intraventricular hemorrhage					
Present	3(20.0)	2(12.5)	1 (2.4)	6 (8.3)	0.088
Absent	12(80.0)	14(87.5)	40(97.6)	66(91.7)	
Focal lesion(s)					
Present	10(66.7)	12(75.0)	14(34.1)	36(50.0)	0.006
Absent	5(33.3)	4(25.0)	27(65.9)	36(50.0)	
Base of skull fracture(s)					
Present	8(53.3)	9(56.3)	10(24.4)	27(37.5)	0.029
Absent	7(46.7)	7(43.8)	31(75.6)	45(62.5)	
Convexity Fracture					
Present	6(40.0)	3(18.8)	12(29.3)	21(29.2)	0.440
Absent	9(60.0)	13(81.3)	29(70.7)	51(70.8)	
Cervical Injury					
Present	1 (6.7)	5(31.3)	0	6 (8.3)	<0.001
Absent	14(93.3)	11(68.8)	41(100.0)	66(91.7)	
Cervical CT					
Done	8(53.3)	10(62.5)	18(43.9)	36(50.0)	0.444
Not done	7(46.7)	6(37.5)	23(56.1)		

Table IV: Mean and standard deviations of difference in the grade of DAI

Category	Mean	Sd	F-statistics	p value
Group A	2.40	0.63	8.66	<0.001
Group B	2.13	0.62		
Group C	1.78	0.42		

A vs C, p < 0.001, B vs C, p = 0.068, A vs B, p = 0.305

Table V: Treatment characteristic of severe traumatic brain injury with diffuse axonal injury

Treatment	Group A [n(%)]	Group B [n(%)]	Group C [n(%)]	Total [n(%)]	P value
Treatment Methods					
Intubation			41(56.9)	41(56.9)	
Ventilation		16(22.2)		16(22.2)	
ICP-CPP Guided	15(20.8)			15(20.8)	
Sedation Status					
No Sedation	0	7(43.8)	26(64.4)	33(45.8)	
Light Sedation	0	7(43.8)	12(29.3)	19(26.4)	
High Sedation	15(100.0)	2(12.5)	3 (7.3)	20(27.8)	
Tracheostomy Status					
Yes	10(66.7)	12(75.0)	19(46.3)	41(43.1)	0.103
No	5 (33.3)	4(25.0)	22(53.7)	31(43.1)	
Usage of Inotrope					
Yes	13(86.7)	6(37.5)	3 (7.3)	22(30.6)	<0.001
No	2 (13.3)	10(62.5)	38(92.7)	50(69.4)	
Usage of Mannitol					
Yes	6 (40.0)	1 (6.3)	7(17.1)	14(19.4)	0.05
No	9 (60.0)	15(93.8)	34(82.9)	58(80.6)	

Table VI: Mean and standard deviations of difference in inotropic usage

Category	Mean	Sd	F-statistics	p value
Group A	0.87	0.35	29.28	<0.001
Group B	0.31	0.50		
Group C	0.07	0.26		

A vs C, p < 0.001, B vs C, p = 0.12, A vs B, p = 0.001

Table VII: Complication of severe traumatic brain injury with diffuse axonal injury

Complication	Group A [n(%)]	Group B [n(%)]	Group C [n(%)]	Total [n(%)]	P value
Pneumonia	6(37.5)	6(50.0)	11(57.9)	23(31.9)	0.569
Sepsis	3(18.8)	1(8.3)	2(10.5)	6(8.3)	0.188
UTI	2(12.5)	2(16.7)	3(15.8)	7(9.7)	0.737
Cardiac Event	1(6.3)	0	0	1(1.4)	0.150
Acute Renal Failure	2(12.5)	0	0	2(2.8)	0.019
Upper GI Bleeding	0	0	2(10.5)	2(2.8)	0.471
Pulmonary Edema	0	1(8.3)	1(5.3)	2(2.8)	0.571
DIVC	1(6.3)	2(16.7)	0	3(4.2)	0.093
DI	1(6.3)	0	0	1(1.4)	0.150

Table VIII: Mean and standard deviations of difference in incidence of pneumonia

Category	Mean	Sd	F-statistics	p value
Group A	0.40	0.51	0.57	0.569
Group B	0.38	0.50		
Group C	0.27	0.45		

A vs C, p = 0.63, B vs C, p = 0.73, A vs B, p = 0.99

Table IX: ICP and CPP readings of severe traumatic brain injury with diffuse axonal injury

Treatment	Mean (SD)	Total [n(%)]
ICP Monitoring		
Mean ICP (mmHg)	15.9(8.24)	
<20mmHg		306(81.6)
20-25mmHg		50(13.3)
25-30mmHg		13 (3.5)
>30mmHg		6 (1.6)
Median ICP	15.00	
Mean CPP(mmHg)	76.9(15.81)	

Table X: Outcome of severe traumatic brain injury with diffuse axonal injury

Outcome	Group A [n(%)]	Group B [n(%)]	Group C [n(%)]	Total [n(%)]	P value
Discharged location					
Home	5 (33.3)	7(43.8)	18(43.9)	30(41.7)	0.001
District Hospital	3 (20.0)	6(37.5)	22(53.7)	31(43.1)	
Death	7 (46.7)	3(18.8)	1 (2.4)	11(15.3)	
GCS upon discharge					
13-15	3 (20.0)	4(25.0)	23(56.1)	30(41.7)	0.003
9-12	3 (20.0)	6(37.5)	12(29.3)	21(29.2)	
3-8	9 (20.0)	6(37.5)	6(14.6)	21(29.2)	
Mean(SD)	7.33(4.791)	9.31(4.51)	12.24(3.50)	10.57(4.46)	<0.001
Survival	8 (53.3)	13(81.3)	40(97.6)	61(84.7)	<0.001
Glasgow Outcome Score					
Upon discharge:					<0.001
Good (4-5)	3 (20.0)	4(25.0)	22(53.7)	29(40.3)	
Poor (2-3)	5 (33.3)	9(56.3)	18(43.9)	32(44.4)	
Death (1)	7 (46.7)	3(18.8)	1 (2.4)	11(15.3)	
Mean(SD)	2.13 (1.45)	2.88(1.03)	3.41(0.74)	3.03(1.05)	<0.001
At 3 months:					
Good (4-5)	6 (75.0)	6(54.6)	27(90.0)	39(79.6)	0.041
Poor (2-3)	1 (12.5)	3(27.3)	3(10.0)	7(14.3)	
Death(1)	1 (12.5)	2(18.2)	0	3 (6.1)	
Unknown(Defaulted)	0	2	10	12	
Mean(SD)	3.88 (1.36)	3.55(1.51)	4.63(0.67)	4.27(1.11)	0.009
At 6 months:					
Good (4-5)	6(100.0)	8(88.9)	30(100.0)	44(97.8)	0.135
Poor (2-3)	0	1(11.1)	0	1 (2.2)	
Death (1)	0	0	0	0	
Unknown(Defaulted)	1	2	10	13	
Mean(SD)	4.67(0.516)	4.56(0.726)	4.83(0.379)	4.76(0.484)	0.291

Table XI: Repeat CT scan brain according to treatment modalities

	Repeat CT scan			
	NO		YES	
	Count	%	Count	%
Group A	6	30.0%	9	17.3%
Group B	2	10.0%	14	26.9%
Group C	12	60.0%	29	55.8%

Table XII: Mean and standard deviations of difference in the repeat CT scan

Category	Mean	Sd	F-statistics	P Value
Group A	0.60	0.507		
Group B	0.88	0.342	1.512	0.228
Group C	0.71	0.461		

A vs C, p = 0.708, B vs C, p = 0.417, A vs B, p = 0.209

Table XIII: Mean and standard deviations of difference in the total numbers of repeat CT scan

Category	Mean	Sd	F-statistics	P Value
Group A	1.20	1.32		
Group B	1.00	0.516	2.784	0.068
Group C	0.71	0.461		

A vs C, p = 0.730, B vs C, p = 0.369, A vs B, p = 0.728

Table XIV: Mean and standard deviations of difference in the length of stay

Category	Mean	Sd	F-statistics	P Value
Group A	11.53	9.04		
Group B	13.31	9.75	2.632	0.079
Group C	8.71	4.99		

A vs C, p = 0.398, B vs C, p = 0.083, A vs B, p = 0.771

Table XV: Mean and standard deviations of difference in the length of ICU stay

Category	Mean	Sd	F-statistics	p value
Group A	8.20	5.89		
Group B	5.88	2.96	4.03	0.022
Group C	4.79	3.45		

A vs C, p = 0.016, B vs C, p = 0.63, A vs B, p = 0.24

Table XVI: Mean and standard deviations of difference in the GCS on admission and discharge

Category	Mean	Sd	F-statistics	p value
Group A	0.47	0.89		
Group B	3.69	0.86	10.03	<0.001
Group C	5.12	0.54		

A vs C, p < 0.001, B vs C, p = 0.34, A vs B, p = 0.30

Table XVII: Prognostic factors of Diffuse Axonal Injury in severe traumatic brain injury by Simple and Multiple Cox Proportional Hazards Model

Variable	Simple Cox Proportional		Multiple Cox Proportional	
	Crude hazards ratio	p-value	Crude hazards ratio	p-value
DAI Grade	4.52(2.12,9.64)	<0.001	4.85(1.98,11.91)	0.001
MAP	0.89(0.82,0.96)	0.002	0.86(0.78,0.94)	0.001
Age Group				
<40 years old	1.00		1.00	0.050
>40 years old	3.27(0.95,11.21)	0.060	3.63(1.00,13.17)	

Forward stepwise Cox Proportional Hazards Regression Model applied

E. Survival Analysis

This survival analysis was done to predict the hazards risk of Diffuse Axonal Injury based on Marshall Classification. The analysis also assessed relationship between covariates and survival time.

There were three factors identified to be significantly affecting the survival of patients with severe traumatic brain injury. These factors were Marshall Grade of the CT scan brain, mean arterial pressure (MAP) and the age group. For each unit increase in Marshall Grade, the hazards of dying are increase by 4.6 times (Table XVII). The hazards of dying are decrease by 0.2 times with each unit increase in mean artery pressure. Meanwhile, the hazards of dying among patients with age group >40 years old are increase by 3.6 times compared to those younger than 40 years old (Table XVII).

DISCUSSION

An impact that transfers energy to the brain at the time of injury can result in varying extent of mechanical, neuronal and axonal damage which are often difficult to salvage. This kind of brain damage is termed as primary brain injury. Secondary brain damage occurs from prospectively treatable conditions such as increased intracranial pressure (ICP), intracranial bleeding, ischemia, hypercarbia, and hypoxia. Maximizing management is of critical importance to minimize secondary brain damage with objective of decreasing overall mortality and improve functional outcome. Despite active management in the treatment of severe traumatic brain injured patients, the mortality and morbidity are still very high[1]. Most severe traumatic brain injury studies revealed high mortality rates between 25-38%[1,6,7].

In our study, focusing on diffuse axonal injury without surgical lesion, the mortality rate was only 15.3%. This signified an importance to have separate studies for all subgroups in severe brain injury, in order to determine the risks and prognostic factors. This will contribute to better understanding of the best treatment modalities for each subgroup as the outcomes were different. The usual practices based on the Brian Trauma Foundation guideline may not be the best option as this study showed a better outcome even in the intubation group which had the least intervention done, but with the lowest mortality rate of 3.4%. There were almost eighty percent of survivals improved to moderate and minimal disability in the first three months of the recovery period. The figure was further improved after six months post injury.

A total of 375 recordings of ICP measurement of all patients treated with ICP-CPP guided management. The mean ICP was 15.96mmHg (SD 8.24). 81.6% of readings were recorded below 20mmHg, 13.3% between 20-25mmHg, 3.5% between 25-30mmHg and only six readings (1.6%) recorded above 30mmHg. The result showed most patients with DAI will have normal ICP readings which were below 20 mmHg. Our result suggests ICP monitoring is not needed in DAI compared with other form of severe traumatic brain injury. This is similar to the study done by Lee *et al.*[8] in 1988, which proposed that a subgroup of patients presenting with severe head trauma and diffuse axonal injury (DAI) without associated mass lesion, do not need ICP monitoring.

Patients who presented with GCS 3 to 5 had worse outcome in comparison to those with admission GCS 6 to 8 ($p = 0.001$). Andrews[9] in 1998 found similar outcome results in patients with DAI. The component of GCS which had significant impact on outcome was motor response. Patients presented with abnormal motor score had worse outcome than those with normal motor score ($p = 0.01$).

The mean days of length of ICU stay were different between all three treatment modalities, where it was higher in ICP-CPP group than the other two groups, and it was statistically significant with ICP-CPP group required a longer ICU stays compared to intubation group ($p = 0.022$).

Outcome upon discharge was worse in the ICP-CPP group which consists of patients with poorer Marshall Grading, poorer GCS and motor response. The mean GOS score was only 2.13 in comparison to intubation and ventilation group with mean GOS score of 3.41 and 2.88 respectively ($p < 0.001$). The mean survival also noted to be smaller in ICP-CPP group and it was statistically significant ($p < 0.001$). This difference was also noted during first three months follow-up but not after six months follow-up. This may suggest the neurological recovery in ICP-CPP group was slower but the improvement after six months was comparable with the other two treatment groups.

Repeat CT scan may be thought to be done less if patient was ICP monitored. However, there was no statistical significant between the need for repeat CT scan and also the numbers of rescanning of all three groups. The findings show ICP monitoring is not a substitute for the need of repeated CT scan in patients with severe brain injury.

In our study, age was proven to be one of the hazards risks of dying. Those aged above 40 years old have increased 3.6 folds risk of dying than those aged below 40 years old. These findings correspond to a study by Susman *et al*[10] where mortality was 24% (2-folds higher) in the elderly population compared to 12.8% in the non-elderly population. Survival analyses have also shown increase in hazards of dying with higher DAI grading. With each unit increase in DAI grade, there is expected to increase risk of dying by 4.6 times. The effect to MAP also found to have independent effect on risk of dying. It was found that each unit of increase MAP expected to decrease the hazards of dying by 0.2 times.

In our study, there was no significant difference in term of outcome between gender ($p = 0.747$). However the number of female patients was small, which may not give an accurate statistical result.

CONCLUSION

A specific treatment plan is needed for patients with diffuse axonal injury. The devastating outcome of patients treated with the best recommended plan shown in this study may alert us if we have done more than what is required. In isolated diffuse axonal injury, the severity of the brain injury may be better than those with associated surgical lesion such as intracerebral hemorrhage. The depressed consciousness resulting in the very poor state of responsiveness may be just due to diffuse injury to the brain, which may recovered better than other parenchymal brain injury.

The limitations of our study are (a) Short follow-up periods which may not reflect the long term outcome (b) Usage of simple Glasgow Outcome Score for outcome assessment which did not assess different type and degree of disabilities. Future study should be done to overcome these limitations.

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