

Outcomes after Traumatic Brain Injury with Concomitant Severe Extracranial Injuries

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Abstract

Traumatic brain injury (TBI) is a leading cause of death and disability in trauma patients. Patients with TBI frequently sustain concomitant injuries in extracranial regions. The effect of severe extracranial injury (SEI) on the outcome of TBI is controversial. For 8 years, we retrospectively enrolled 485 patients with the blunt head injury with head abbreviated injury scale (AIS) ≥ 3 . SEI was defined as AIS ≥ 3 injuries in the face, chest, abdomen, and pelvis/extremities. Vital signs and coagulation parameter values were also extracted from the database. Total patients were dichotomized into isolated TBI ($n = 343$) and TBI associated with SEI ($n = 142$). The differences in severity and outcome between these two groups were analyzed. To assess the relation between outcome and any variables showing significant differences in univariate analysis, we included the parameters in univariable and multivariable logistic regression analyses. Mortality was 17.8% in the isolated TBI group and 21.8% in TBI with SEI group ($P = 0.38$), but the Glasgow Outcome Scale (GOS) in the TBI with SEI group was unfavorable compared to the isolated TBI group ($P = 0.002$). Patients with SBP ≤ 90 mmHg were frequent in the TBI with SEI group. Adjusting for age, GCS, and length of hospital stay, SEI was a strong prognostic factor for mortality with adjusted ORs of 2.30. Hypotension and coagulopathy caused by SEI are considerable factors underlying the secondary insults to TBI. It is important to manage not only the brain but the whole body in the treatment of TBI patients with SEI.

Key words: traumatic brain injury, extracranial injury, mortality, prognosis, prognostic model

Introduction

High impact trauma frequently causes damage to multiple body regions and organs. Severe traumatic brain injury (TBI) is known to be a leading cause of death and disability.¹ About one-third or half of TBI cases have associated severe extracranial injury (SEI) in the chest, abdomen, and extremities.^{2–3} Many authors have reported that SEI with concomitant head injury is associated with high mortality rates.^{4–6} In contrast to these reports, the influence of extracranial injury on the outcome of TBI remains controversial.^{7–10} In patients with brain injury, concomitant injuries in extracranial sites cause decreased cerebral blood flow and/or coagulopathy due to massive hemorrhage as secondary brain damage.¹¹

We conducted a retrospective observational single-center study of TBI with or without SEI to determine the magnitude of the influence exerted

by extracranial injury on head injury. The primary objective of this study was to examine the influence of concomitant SEI on the mortality or functional outcome of brain injury. We hypothesized that patients with TBI and SEI would have worse outcomes and that therefore the mitigation of secondary brain damage to TBI would be an important objective for future interventions.

Materials and Methods

Patient population and data collection

In our database, each injury is evaluated according to the abbreviated injury scale (AIS) with scores ranging from one to six, with one being the least severe six body regions (head, face, chest, abdomen, pelvis/extremities, and external). We retrospectively extracted patients with the blunt head injury with head AIS ≥ 3 admitted to the emergency and critical care center of Nara Medical University within 6 h of a severe TBI during the 8-year period April 1, 2007 to March 31, 2015 from the electronic medical records system. All patients were treated basically in accordance with the unified treatment and management strategies of the hospital. We used the Japan

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Society of Neurotraumatology (JNST) guideline for head trauma and the Japan Advanced Trauma Evaluation and Care (JATEC) for multiple trauma as the standardized management and treatment protocol. The treatment principle is to give priority to the body sites, including the head that is at the greatest life-threatening risk.

Patients who died in the emergency room were not included in the study. We also excluded the patients who had AIS 6 injury, only basal skull fracture without intracranial lesions, spinal cord injury, and cardiopulmonary arrest on site. For the purposes of this study, SEI was defined as AIS \geq 3 injuries in the face, chest, abdomen, and pelvis/ extremities. Vital signs and coagulation parameters were also extracted from the database. This study was performed in accordance with the guideline of the Ethics Committee of Nara Medical University. Because of this retrospective nature of the study, the Committee decided that informed consent from patients would not be necessary only by posting the research contents in the hospital.

Trauma severity

The severity of systemic injuries including TBI was expressed according to the following parameters: Injury severity score (ISS) as an anatomical scoring system, revised trauma scale (RTS) as a physiological scoring system, the probability of survival (Ps) calculated from age, ISS, and RTS, and length of hospital stay. The severity of TBI was mainly determined by the Glasgow Coma Scale (GCS).

Outcome

Outcome was evaluated using the GOS at hospital discharge. GOS consists of five categories (GR: good recovery = 1, MD: moderate disability = 2, SD: severe disability = 3, PVS: persistent vegetative state = 4, and D: dead = 5). The primary outcome for this study was mortality at discharge and the second was unfavorable outcome. We defined GR and MD as favorable and the others (SD, PVS, and D) as unfavorable to the functional outcome.

Statistical analysis

We described the patients' basic characteristics with standard summary statistics. Categorical variables were reported as frequency and percentage, and continuous variables as the median with interquartile range (IQR) or mean with standard deviation (SD) in vital signs. Total patients ($n = 458$) were dichotomized into isolated TBI ($n = 343$) and TBI associated with SEI ($n = 142$). The differences in severity and outcome between these two groups were analyzed. According to the distribution and types of variables,

different methods of univariate analysis were used for preliminary screening factors influencing the outcome. Mann–Whitney *U*-test, Fisher's exact test, and chi-square test were performed to identify differences between the dichotomous groups. Risk factor variables with a $P < 0.2$ in the univariate analysis were included in a forward stepwise logistic regression. We performed univariable and multivariable logistic regression analyses to identify independent predictors for overall mortality and unfavorable outcome. All tests were two-sided, with P -values of <0.05 considered statistically significant. The statistical analyses were performed using Bell Curve for Excel 2016 (Social Survey Research Information, Tokyo, Japan).

Results

Patient baseline characteristics on admission

The TBI with SEI group comprised 142 patients accounting for 29.3% of the total. The mean age was in the early 6th decade in both groups, and though a male predominance was seen, no significant difference was found in this between them (Table 1). With regard to vital signs, heart rate, and respiratory rate were higher in the TBI with SEI group, while systolic blood pressure was higher in the isolated TBI group. Also, since the proportion of patients with systolic blood pressure ≤ 90 mmHg was higher in the TBI with SEI group (13.4%), it was surmised that this group included many patients in a shock state or hyperventilating to compensate for metabolic acidosis. Regarding the mechanism of injury, in the isolated TBI group traffic accidents predominated (49.6%, with violence implicated in many of the remaining cases. The diagnosis of head injuries was classified as acute sub- or epidural hematoma, brain contusion, traumatic subarachnoid hemorrhage, and diffuse axonal injury.

The frequency of acute hematoma in the isolated TBI group was significantly higher than that in TBI with SEI group (Table 1). In the TBI with SEI group, in addition to the head, the chest, abdomen, extremities, and pelvis often showed injuries, and so the frequency of surgery in this group was high. The incidence of epidural and/or subdural hematoma was significantly higher in the isolated TBI group, whereas DAI was significantly higher in the TBI with SEI group. The frequency of total surgical treatments was significantly higher in the TBI with SEI group. The frequency of brain surgery was 30.6% in the isolated TBI group and 21.8% in the TBI with SEI group. The isolated TBI group showed a tendency to a higher incidence ($P = 0.06$) of brain surgery.

Table 1 Baseline characteristics of the 485 study patients

	Total	Isolated TBI	TBI with SEI	<i>P</i>
	<i>n</i> = 485	<i>n</i> = 343	<i>n</i> = 142	
Age	51.3(26.7)	50.9(27.9)	52.1(23.7)	0.92
Mean (SD), <i>y</i>				
Gender	338(70.1)	240(70.4)	98(69.5)	0.91
Male, <i>n</i> (%)				
Vital signs mean (SD)				
Heart rate./min	91.6(25.5)	89.8(25.1)	95.8(26.1)	0.002
SBP, mmHg	146.0(42.2)	152.5(40.3)	130.3(42.5)	<0.001
SBP ≤ 90 mmHg, <i>n</i> (%)	32(6.6)	13(3.8)	19(13.4)	<0.001
Respiratory rate./min	20.9(6.3)	20.1(6.1)	22.8(6.4)	<0.001
Mechanism, <i>n</i> (%)				
Traffic accident	267(55.1)	170(49.6)	97(68.3)	<0.001
Fall	123(25.4)	88(25.7)	35(24.6)	0.9
Heavy object	8(1.6)	4(1.2)	4(2.8)	0.2
Unknown	11(2.3)	10(2.9)	1(0.7)	0.2
Others	76(15.7)	71(20.6)	5(4.0)	<0.001
Head injury diagnosis, <i>n</i> (%)				
ASDH and/or AEDH	236(48.7)	180(52.5)	56(39.4)	<0.01
Contusion	101(20.8)	73(21.3)	28(19.7)	0.81
tSAH	71(14.6)	46(13.4)	25(17.6)	0.26
DAI	66(13.6)	38(11.1)	28(19.7)	0.014
Others	11(2.3)	6(1.7)	5(3.5)	0.31
Operation, <i>n</i> (%)				
Total	220(45.4)	127(37.0)	93(65.5)	<0.001
Head	136(28.0)	105(30.6)	31(21.8)	0.06

ASDH: acute subdural hematoma, AEDH: acute epidural hematoma, DAI: diffuse axonal injury, SEI: severe extracranial injuries, tSAH: traumatic subarachnoid hemorrhage, TBI: traumatic brain injury. Data are indicated mean with standard deviation (SD).

Traumatic severity in TBI and SEI

Patient distribution of AIS in the TBI with SEI Group was shown in Table 2. The frequency decreased in the order of head, chest, pelvis/extremities, abdomen, and face. Head trauma was frequently associated with the serious chest injury (Table 2).

Although on presentation the GCS scores did not differ between the two groups (median scores 11 or 12) (Table 3), the fact that the median scores were 11 or 12 indicates that many patients with mild brain injury were present in both the groups. Head AIS did not differ between the two groups. In the TBI with SEI group, ISS was of course high due to the presence of multiple injuries, and because of the influence of high values of ISS. The median Ps values (score 0.82) were significantly lower in the TBI with SEI group. Reflecting the fact that the two groups did not show significant differences in either GCS or age, no difference was noted in RTS either. The median length of hospital stay in the isolated TBI group was 14 days (IQR: 6–30.5) and considerably longer at

Table 2 Patient's distribution of AIS in TBI with SEI group (*n* = 142)

AIS	Five body regions				
	Head	Face	Chest	Abdomen	Pelvis/Ext
1	No entry	4	3	0	0
2	No entry	5	4	14	32
3	52	1	47	17	51
4	34	1	40	6	4
5	56	0	4	1	2
Total	142	11	98	38	89

AIS: abbreviated injury scale, Ext: extremities.

31 days (IQR: 14–57) in the TBI with SEI group. This longer stay was thought to reflect the necessity for continuing treatment of trauma at sites other than the head. Patients with SBP ≤ 90 mmHg thought to indicate the presence of hemorrhagic shock were more frequent in the TBI with SEI group (*P* < 0.001).

Table 3 Trauma severity and related parameters

	Total		Isolated TBI		TBI with SEI		<i>P</i>
	<i>n</i> = 485		<i>n</i> = 343		<i>n</i> = 142		
	Median	IQR	Median	IQR	Median	IQR	
GCS on arrival	11	(6–15)	12	(6–15)	11	(6–14)	0.13
AIS of head	4	(3–5)	4	(3–5)	4	(3–5)	0.53
ISS	25	(16–28)	17	(13–25)	34	(25–41)	<0.001
RTS	6.90	(5.97–7.84)	6.90	(5.97–7.84)	6.90	(5.29–7.84)	0.104
Ps	0.93	(0.68–0.97)	0.95	(0.82–0.98)	0.82	(0.46–0.94)	<0.001
Length of hospital stay, day	18	(7–39)	14	(6–30.5)	31	(14–57)	<0.001
Coagulation							
Platelets, 10 ⁴ /μl	21.2	(17.1–25.6)	21.4	(17.3–25.8)	20.5	(16.8–25.1)	0.40
PT (s)	12.0	(11.3–12.9)	11.8	(11.2–12.6)	12.5	(11.7–13.4)	<0.001
PT-INR	1.03	(0.98–1.12)	1.02	(0.96–1.10)	1.07	(1.0–1.18)	<0.001
aPTT (s)	27.2	(25.0–31.2)	27.7	(25.0–30.9)	27.7	(25.3–32.6)	0.07
FDP, μg/ml	55.5	(21.1–157.0)	41.2	(15.0–129.2)	90.9	(41.0–226.3)	<0.001
D-dimer, μg/ml	32.6	(12.8–95.0)	24.4	(8.1–70.1)	57.8	(23.3–133.2)	<0.001

AIS: abbreviated injury scale, aPTT: activated partial thromboplastin time, FDP: fibrin/fibrinogen degradation products, GCS: Glasgow Coma Scale, ISS: injury severity score, IQR: interquartile range, Ps: probability of survival, PT: prothrombin time, PT-INR: prothrombin time-international normalized ratio, RTS: revised trauma score, SEI: severe extracranial injury, TBI: traumatic brain injury. Data are indicated median and IQR.

All coagulation parameters with the exception of platelet counts showed significantly higher values in the TBI with SEI group. In particular, the median fibrin/fibrinogen degradation products (FDP) and D-dimer values were 2–2.5-fold higher, and were thought to reflect hypercoagulation and hyperfibrinolysis associated with massive hemorrhage in the TBI with SEI group.

Outcome

Mortality was 17.8% in the isolated TBI group, and 21.8% in the TBI with SEI group ($P = 0.38$). On the other hand, regarding GOS, in the isolated TBI group, GR was seen in close to one-half of cases (46.9%) while in the TBI with SEI group the proportion of MD was highest at 36.6%. When the functional outcome including death was compared using GOS it was found to be better in the isolated TBI group than in the TBI with SEI group ($P = 0.002$) (Table 4).

Univariable and multivariable predictive models for mortality or unfavorable outcome

To determine the influence of SEI on mortality, a univariable analysis was performed with the presence/absence of SEI as the explanatory variable and mortality as the dependent variable, with the OR found to be 1.29 (95%CI, 0.780–2.10) and the R^2 -value was 0.002 (Table 5). Next, a multivariable analysis was performed with age, GCS, length of

Table 4 Outcome

	Isolated TBI	TBI with SEI	<i>P</i>
	<i>n</i> = 343	<i>n</i> = 142	
No of death (mortality, %)	61(17.8)	31(21.8)	0.38
GCS \geq 9 on arrival, <i>n</i> (%)	4(1.2)	6(4.2)	0.081
GOS [score], <i>n</i> (%)			
GR ⁽¹⁾	11(46.9)	43(30.3)	0.002
MD ⁽²⁾	96(28.0)	52(36.6)	
SD ⁽³⁾	15(4.4)	8(5.6)	
PVS ⁽⁴⁾	10(2.9)	8(5.6)	
D ⁽⁵⁾	61(17.8)	31(21.8)	

D: dead, GCS: Glasgow Coma Scale, GR: good recovery, MD: moderate disability, PVS: persistent vegetative state, SD: severe disability, SEI: severe extracranial injury, TBI: traumatic brain injury.

hospital stay, and presence of SEI as the explanatory variables. OR of SEI was calculated as 2.30 (95%CI, 1.03–5.14) and the R^2 -value of the model was 0.41. Based on the result, we concluded that SEI is an independent prognostic factor for mortality in TBI patients.

In addition to clarify the relation between the neurological outcome of head trauma and SEI, a multivariable analysis was performed with unfavorable

outcome (defined as SD, PVS, and D) as the dependent variable, and age, GCS, length of hospital stay, and presence/absence of SEI as the explanatory variables. OR of SEI was 1.62 (95%CI, 0.91–2.89) and the R^2 -value was 0.38 (Table 5). In this model, only age and GCS are an independent prognostic factor for unfavorable outcome in TBI patients.

Discussion

This study was undertaken to characterize the influence of SEI sustained at the same time as head trauma on the outcome of the latter. Head trauma is known to be associated with SEI in 23%–48%^{2,3,12,13} of cases, and 29.3% in our own series. This wide range of frequencies is attributable to differences in the study populations, study protocols, and definitions of SEI used in the various investigations.^{5,8,10} We consider that our definition used here, namely SEI associated with AIS ≥ 3 extracranial injuries should be adopted. Significant differences were identified in the developmental mechanisms of the two groups studied here. In high impact traffic injury, SEI frequently accompanies head trauma, with the most significant SEI involving the chest, pelvis/extremities, and abdomen. On the other hand, since in the isolated TBI group, other underlying mechanisms include person-to-person violence that selectively injures mostly the head, injuries sustained in traffic accidents are relatively few in number.

Hitherto as well, the outcome of injury cases including TBI and not including TBI (namely, SEI alone) has been compared. In many of such reports, head trauma has been demonstrated to be the major factor predictive of mortality. Gennarelli et al. showed that as compared with SEI alone cases not including TBI, injury including TBI showed a 3-fold higher mortality rate.⁵ We consider the

contention that head trauma is the major outcome-determining factor in multiple injury cases to be correct. However, it must also be noted that only a few studies have focused on comparisons of outcome between isolated TBI and TBI with SEI. In the report of Sarrafzadeh on cases with GCS ≤ 8 head trauma, the mortality rate of TBI with SEI was 25% and that of isolated TBI 29%, with the latter being higher but not significantly so.¹⁰ In this report, no significant difference was noted in GOS 1 year later. In our present report, mortality rate was 17.8% in isolated TBI and 21.8% in TBI with MEI, with this difference not significant. In contrast, with regard to GOS, which includes the element of functional outcome, Isolated TBI group showed better results. These results show that in a comparison of the two groups, the presence of SEI does not have sufficient impact to significantly increase mortality, with the severity of head trauma as assessed by GCS and other tools having a greater influence. And we consider that the worse the GCS score the more attenuated becomes the impact of SEI.

Next, the results of the present multiple logistic model demonstrated that SEI is an independent outcome-determining factor of head trauma. Mortality in the multivariable analysis showed an OR of 2.3, and unfavorable outcome including death and disability OR of 1.62. In a report of a meta-analysis including TARN (Trauma Audit and Research Network),^{14–17} which is a registry encompassing all head trauma from immediately after injury, after adjusting for age, GCS motor score, and pupil reactivity, the presence of SEI was strongly correlated with mortality. In this analysis, stratification according to GCS was done and revealed that the greater the severity of head trauma became the less impact of SEI: mild (GCS 13–15) OR = 2.81, moderate (GCS 9–12) OR = 2.18, severe (GCS 3–8) OR = 2.14.¹⁵ Mortality

Table 5 Independent risk factors for mortality and unfavorable outcome

	Prognostic variables	OR	95%CI		P	R^2
Mortality	SEI (multivariable)	2.30	1.03	5.14	0.042*	0.414
	Age	1.03	1.01	1.04	<0.001**	
	GCS	0.63	0.57	0.70	<0.001**	
	Length of Hp stay	0.95	0.94	0.97	<0.001**	
	SEI (univariable)	1.29	0.80	2.10	0.302	
Unfavorable outcome (GOS = D, PVS, SD)	SEI (multivariable)	1.62	0.91	2.89	0.099	0.374
	Age	1.03	1.02	1.04	<0.001**	
	GCS	0.68	0.63	0.73	<0.001**	
	Length of Hp stay	0.99	0.99	1.00	0.053	
	SEI (univariable)	1.48	0.97	2.26	0.072	

CI: confidence intervals, GCS: Glasgow Coma Scale, OR: Odds ratio, PVS: persistent vegetative state, R^2 : Cox & Snell R^2 , SEI: severe extracranial injuries. * $P < 0.05$, ** $P < 0.01$.

within 6 h of sustaining head trauma is analyzed to be one factor underlying the strength of this correlation. Since the number of cases available for study in the present work was small as compared to TARN, it was not possible to stratify the severity of head trauma, but we consider that had the number of cases been increased same result would have been yielded. Also, since outpatient deaths and cases sustaining cardiopulmonary arrest after injury were excluded, fatal cases within 2–3 h of injury were not included, but had it been possible to include them SEI would likely have been found to be an even more potent outcome-determining factor.

In examining the relationship between mortality and prognostic factors including SEI, the causes of death in the study groups need to be considered. In the case of multiple trauma patients, the cause of death is generally difficult to determine. In the case of brain death, we have experienced many cases, in which it was impossible to attribute the cerebral perfusion failure to either hypotension caused by hemorrhagic shock or to low cerebral perfusion pressure caused by high intracranial pressure. As our study population consisted of hospitalized patients after successful fluid resuscitation in the emergency room, fatal cases with hemorrhagic shock were very few. Our study group included total of 92 cases of death, in which patients with $GCS \leq 8$ were surmised to have sustained severe impact to the head. They were thought to have had a general condition stable enough that the cause of death after hospitalization was head trauma. We found 10 fatal patients with $GCS \geq 9$ on arrival: 4 in the isolated TBI Group (1.2%) and 6 (4.2%) in TBI with SEI Group. Six cases in the TBI with SEI Group, with brain lesions of AIS over 3, developed a rapidly decreased consciousness level in the emergency room and had the possibility of death caused by head trauma.

In the results, significant differences in the type and frequency of TBI were observed between the two groups. Epidural and/or subdural hematoma frequently occurred in the isolated TBI group and DAI in the TBI with SEI group. The reason is thought to be due to the difference between the focus of the traumatic impact directed to the head in contrast to the overall body, which means that isolated TBI causes focal brain injury, while the TBI associated with SEI is likely to manifest diffuse brain injury. Also, differences in the treatment may affect the outcome. The frequency of total surgical treatments was significantly higher in the TBI with SEI group, while the frequency of the surgery limited to the brain tended to show a higher incidence ($P = 0.06$) in the isolated TBI group. Since the difference in GOS between the two groups was not significant,

we concluded that the effects of the differences in TBI types and in the surgical treatments on the results of this study would be small.

Since on arrival GCS did not differ between the 2 groups in the present study, the primary insult due to head trauma was equivalent severity. However, in the TBI with SEI group, the frequency of hypotension, hypoxia, and coagulopathy attributable to SEI and the total injury severity were higher than in the isolated TBI group. The injured brain in the TBI with SEI group would seem to be more vulnerable to such secondary insults. In the TBI with SEI group, the laboratory values related to coagulation other than platelet count were markedly abnormal. Thrombocytopenia, PT, and D-dimer abnormalities are independent risk factors of cerebral ischemia after injury that have been reported to worsen the outcome of head trauma.¹⁸⁾ In the present study, the presence/absence of cerebral ischemia after injury was not determined, but the presence of coagulation abnormalities may have been another factor worsening outcome in the TBI with SEI group.

Although reported studies are limited,¹⁹⁾ secondary insults are thought to induce neuroinflammation, in this way, adversely affecting the outcome of the TBI with SEI group. In recent experiments on head trauma in a mouse model, in the group sustaining repeated bone fractures as compared to isolated TBI cerebral edema was extensive, and the neurological prognostic score was unfavorable.²⁰⁾ The authors reported that in the multiple bone fracture, group blood cytokine concentrations were high with the bone fractures enhancing cytokine release and worsening the outcome. Moreover, in the head trauma plus bone fracture group as compared with the head trauma alone group, the level of the inflammation mediator HMGB1 was elevated, while the outcome was reported to be improved by anti-HMGB1 administration.²¹⁾

In the present study, the functional outcome in the TBI with SEI group was found to be worse than that in the isolated TBI group. This was attributed to the secondary insults, such as hypotension and worsening of coagulopathy induced by the presence of SEI. Various therapeutic strategies including hypothermia have been attempted to improve the outcome of head trauma, albeit without any hard evidence of their effectiveness. Future studies will need to focus on the mitigation of secondary insults in TBI with SEI,¹³⁾ for example, by devising novel strategies to modulate neuroinflammation.

Conclusion

SEI is an independent prognostic factor for mortality in TBI patients. Hypotension and coagulopathy

caused by SEI are considerable factors underlying the secondary insults to TBI. It is important to manage not only the brain but also the whole body including systemic circulation and coagulation in the treatment of TBI patients with SEI.

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Conflicts of Interest Disclosure

The authors have no conflicts of interest regarding this article.

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