Progressive Neurological Deterioration in Mild Traumatic Brain Injury with Acute Intracranial Hemorrhage: A Single Center, Retrospective Observational Comparative Study

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Objective: To assess the rate of acute neurologic aggravation of mild traumatic brain injury (TBI) patients, and to compare the deterioration frequency between categorized admission characteristic groups and the mean values between deteriorated and non-deteriorated groups. **Methods:** From Jan. 2014 to Aug. 2017, medical records of mild TBI patients (Glasgow Coma Scale ≥ 13 on arrival) were retrospectively reviewed. Admission characteristics and neurologic outcome of the first treatment week were analyzed. We compared the frequency of progressive deteriorated patients between independent variable groups and also mean value of admission characteristics between deteriorated and non-deteriorated groups. **Results:** The 193 patients were included in this study. 22 showed neurologic aggravation in the first treatment week. Subdural hematoma (SDH; n=82, 42.5%) was the most frequent CT finding as main lesion. The thickness of epidural hematoma (EDH) or SDH, midline shift and compression of basal cistern in the initial CT scan were significant factors of progressive deterioration, whereas the volume of intracranial hemorrhage (ICH) showed no significance. In laboratory tests, deteriorated group had low hemoglobin (Hb) level and higher white blood cell count. However, the initial vital signs didn't significantly affect the outcome. **Conclusion:** In this study, thickness of EDH or SDH in the initial CT scan, coagulopathy, leukocytosis, anemia showed to have effect on neurologic aggravation. Systolic blood pressure and body temperature, which have been considered important in managing severe TBI patients, showed no significance. However, because the difference is not large enough for clinical use, further studies are needed for verification.

Key Words: Brain injuries, traumatic; Clinical laboratory techniques; Intracranial hemorrhages; Prognosis

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INTRODUCTION

Traumatic brain injury (TBI) is one of the leading cause of mortality and morbidity throughout the world and it is a major socioeconomic problem²⁹⁾. Although the management for TBI has been evolving greatly with a long historical background, the 'heterogeneity of TBI' makes clinicians difficult to establish treatment strategy and to predict outcomes. However, studies about clinical course of acute mild TBI have been difficult to find in the literature as compared to active researches of severe TBI.

Predicting clinical course of acute mild TBI is important, in several point of view. The patient who shows progressive deterioration after good neurological status in the first examina-

tion can be neglected by medical staffs or have more chance to be exposed to monitoring failure compared to those having poor mentality from the first, which may lead to miss the adequate time of neurosurgical and critical care interventions. Because the number of intensive care unit (ICU) beds and medical staff is scarce, we must decide whether these patients should be admitted to the ICU or general ward, or transfer to higher trauma center^{23,25)}. In addition, preventing unnecessary ICU admission reduces cost and prevents potential adverse effect of ICU stay such as delirium and nosocomial infections¹⁷⁾.

The purpose of this study is to assess the rate of progressive mental deterioration of acute mild TBI patients with intracranial hemorrhage within first treatment week who had 6 points of Glasgow Coma Scale (GCS) motor score on arrival at the emer-

gency room (ER), and to compare the deterioration frequency between categorized admission variable groups and the mean values between deteriorated and non-deteriorated groups.

MATERIALS AND METHODS

1. Patients

From January 2014 to August 2017, medical records of TBI patients who initially showed GCS 13 or more on arrival were collected. Among them, patients aged 15 years or more and with history of trauma within 1 week were included in the study. Patients without any traumatic intracranial hemorrhage and those having only linear skull fractures without intracranial lesions were excluded, because they rarely need hospitalization and neurosurgical interventions^{4,11,12,15,16,21,22}. The inclusion and exclusion criteria are as follows.

Inclusion Criteria

- * Patients with 15 or more age.
- * History of head trauma was less than 1 week.
- * Patients with acute intracranial hemorrhage in first computed tomography (CT) scan.
- * Patients who showed 13 or more GCS at first neurological examination at the ER.
- * Patients who showed 6 points of GCS motor score at first.
- * Patients who had been observed for 1 week or more.

Exclusion Criteria

- * Patients who had been discharged from the ER or been immediately transferred to another center.
- * Age below 15.
- * Patients with head trauma history 1 week or more.
- * Patients without acute intracranial hemorrhage in the first CT scan (with or without skull fracture).
- * Patients who showed GCS less than 13 at first neurological examination.
- * Patients who showed 5 or less points of GCS motor score at first examination.
- * Patients who had been observed less than 1 week.
- * Patients who underwent neurosurgical treatment before their neurological progression.

Their age, gender, past medical history (hypertension, diabetes, hematologic disorders, chronic liver diseases, chronic kidney diseases, presence of solid cancer, antiplatelet and anti-coagulant medication), initial vital signs (systolic blood pressure [SBP], pulse rate [PR], respiratory rate [RR], body temperature [BT]), initial laboratory results (white blood cell [WBC] count, hemoglobin [Hb] level, platelet count [PC], prothrombin time [PT], activated partial thromboplastin time [aPTT]), first CT findings (type of hemorrhage, dominant hemorrhage type, dominant side, volume of hemorrhage, midline shift, presence of skull fracture, compression of basal cistern), initial GCS, injury to CT time and acute neurological outcome during the first treatment week were analyzed. Reduction of the GCS motor

score was considered as symptomatic progression.

2. Statistical Analysis

Each independent variable was grouped to compare the frequency of exacerbated patients between groups. The grouping of each independent variable was made with the values shown in the Table 1. In addition, the mean values of the continuous variables of the deteriorated group and the non-deteriorated group were compared. Statistical analysis was performed with SAS/STAT[®] software (SAS Institute Inc., Cary, NC, USA) using χ^2 or Fisher's exact test in frequency comparison and Wilcoxon's or *t*-test in the mean comparison, according to the type of the variables.

RESULTS

1. Baseline Information of the Patients

With above listed inclusion and exclusion criteria, 193 consecutive patients were included in the study. Among these patients, 22 patients (11.4%) showed neurological aggravation in the first treatment week. Baseline information of the patients are described in Table 1 and mean values of each variables are in Table 2. Mean age was 64.89 ± 17.36 and 75 patients (38.9%) were female. The 87 patients had hypertension and 51 had diabetes. Six patients had hematologic disorders. Two patients had chronic liver disease and 13 patients had chronic kidney disease. The 7 patients were under treatment of solid cancer. Forty-nine patients were having at least one antiplatelet agents and 5 patients were under anticoagulation. Mean GCS was 14.53 ± 0.71 . Mean SBP, PR, RR, and BT on arrival were 141.30 ± 23.37 mmHg, 81.15 ± 15.23 /min, 18.39 ± 2.72 /min, and 36.71 ± 0.52 °C. Initial WBC count, Hb, PC, PT international normalized ratio [INR], and aPTT were $8,175 \pm 3,54$ 10^9 /L, 232.54 ± 76.05 10^9 /L, 1.05 ± 0.10 and 27.86 ± 7.73 sec. The mean time taken for CT scanning since trauma was 17.90 ± 30.99 (0.5-164) hr. Subdural hematoma (SDH; n=82, 42.5%) was the most frequent CT finding as a main lesion followed by intracerebral hemorrhage (ICH; n=59, 30.6%), subarachnoid hemorrhage (SAH; n=31, 16.1%), epidural hematoma (EDH; n=21, 10.9%). Eighty-two patients had left side dominant lesion (42.5%). Forty patients showed at least 1 mm of midline shift and 57 patients had concomitant skull fractures. Compressed basal cisterns were noted in 10 patients.

2. Comparison of the Frequency of Deteriorated Patients between Independent Variable Groups

We compared the frequency of progressive deteriorated patients between independent variable groups (Table 1). Male, GCS, WBC over 10.0×10^9 /L, Hb less than 12 g/dL, aPTT over 40 sec, presence of SDH or SAH, thicker EDH or SDH, more

Table 1. Baseline characteristics of the patients and frequency comparison of deteriorated patients between independent variable categories (continued)

Admission characteristics	Category	All patients (n=193)	Deteriorated (n=22)	Non-deteriorate d (n=171)	p-value
Age (year)	<65	81 (42.0)	6 (27.3)	75 (43.9)	0.138
	≥65	112 (58.0)	16 (72.7)	96 (56.1)	
Sex	Male	118 (61.1)	18 (81.8)	100 (58.5)	0.035 [†]
	Female	75 (38.9)	4 (18.2)	71 (41.5)	
History					
Hypertension	Yes	87 (45.1)	10 (45.5)	77 (45.0)	0.970
	No	106 (54.9)	12 (54.5)	94 (55.0)	
Diabetes	Yes	51 (26.4)	9 (40.9)	42 (24.6)	0.102
	No	142 (73.6)	13 (59.1)	129 (75.4)	
Hematologic disorder	Yes	6 (3.1)	1 (4.5)	5 (2.9)	0.521 [*]
	No	187 (96.9)	21 (95.5)	166 (97.1)	
Chronic liver disease	Yes	2 (1.0)	0 (0.0)	2 (1.2)	1.000 [*]
	No	191 (99.0)	22 (100.0)	169 (98.8)	
Chronic kidney disease	Yes	13 (6.7)	3 (13.6)	10 (5.8)	0.172 [*]
	No	180 (93.3)	19 (86.4)	161 (94.2)	
Solid cancer	Yes	7 (3.6)	0 (0.0)	7 (4.1)	1.000 [*]
	No	186 (96.4)	22 (100.0)	164 (95.9)	
Antiplatelet agent	Yes	49 (25.4)	8 (36.4)	41 (24.0)	0.209
	No	144 (74.6)	14 (63.6)	130 (76.0)	
Anticoagulant	Yes	5 (2.6)	0 (0.0)	5 (2.9)	1.000 [*]
	No	188 (97.4)	22 (100.0)	166 (97.1)	
Trauma to CT time	≤2	75 (38.9)	7 (31.8)	68 (39.8)	0.485
	>2 and ≤8	50 (25.9)	8 (36.4)	42 (24.6)	
	>8	68 (35.2)	7 (31.8)	61 (35.7)	
GCS score	15	126 (65.3)	8 (36.4)	118 (69.0)	0.003 ^{*,†}
	14	43 (22.3)	7 (31.8)	36 (21.1)	
	13	24 (12.4)	7 (31.8)	17 (9.9)	
Vital signs					
Systolic blood pressure (mmHg)	≥140	47 (24.4)	7 (31.8)	40 (23.4)	0.560
	≥90 and <140	136 (70.5)	13 (59.1)	123 (71.9)	
	<90	10 (5.2)	2 (9.1)	8 (4.7)	
Pulse rate (per min)	≥100	27 (14.0)	5 (22.7)	22 (12.9)	0.339 [*]
	≥60 and <100	158 (81.9)	16 (72.7)	142 (83.0)	
	<60	8 (4.1)	1 (4.5)	7 (4.1)	
Respiratory rate (per min)	≥20	86 (44.6)	12 (54.5)	74 (43.3)	0.317
	<20	107 (55.4)	10 (45.5)	97 (56.7)	
Body temperature (°C)	≥37.5	18 (9.3)	1 (4.5)	17 (9.9)	0.699 [*]
	<37.5	175 (90.7)	21 (95.5)	154 (90.1)	

CT: computed tomography; GCS: Glasgow Coma Scale; WBC: white blood cell; PT: prothrombin time; INR: international normalized ratio; aPTT: activated partial thromboplastin time; SDH: subdural hematoma; ICH: intracerebral hemorrhage; EDH: epidural hematoma; SAH: subarachnoid hemorrhage; IVH: intraventricular hemorrhage.

The data is presented as number (%).

^{*}p-value by Fisher's exact test. [†]p<0.05.

Table 1. Baseline characteristics of the patients and frequency comparison of deteriorated patients between independent variable categories

Admission characteristics	Category	All patients (n=193)	Deteriorated (n=22)	Non-deteriorate d (n=171)	p-value
Laboratory findings					
WBC count (10 ⁹ /L)	>10.0	43 (22.3)	10 (45.5)	33 (19.3)	0.012 ^{*,†}
	≤10.0	150 (77.7)	12 (54.5)	138 (80.7)	
Hemoglobin (g/dL)	≥12	117 (60.6)	8 (36.4)	109 (63.7)	0.013 ⁺
	<12	76 (39.4)	14 (63.6)	62 (36.3)	
Platelet count (10 ⁹ /L)	≥150	171 (88.6)	19 (86.4)	152 (88.9)	0.063 [*]
	≥100 and <150	18 (9.3)	1 (4.5)	17 (9.9)	
	<100	4 (2.1)	2 (9.1)	2 (1.2)	
PT (INR)	>1.2	9 (4.7)	2 (9.1)	7 (4.1)	0.273 [*]
	≤1.2	184 (95.3)	20 (90.9)	164 (95.9)	
aPTT (sec)	>40	7 (3.6)	4 (18.2)	3 (1.8)	0.004 ^{*,†}
	≤40	186 (96.4)	18 (81.8)	168 (98.2)	
CT findings					
Hemorrhage type (if any)	SDH	116 (60.1)	21 (95.5)	95 (55.6)	<0.001 ⁺
	ICH	81 (42.0)	12 (54.5)	69 (40.4)	0.204
	EDH	26 (13.5)	3 (13.6)	23 (13.5)	1.000 [*]
	SAH	106 (54.9)	18 (81.8)	88 (51.5)	0.007 ⁺
	IVH	2 (1.0)	0 (0.0)	2 (1.2)	1.000 [*]
Dominant lesion type	SDH	82 (42.5)	13 (59.1)	69 (40.4)	0.319 [*]
	ICH	59 (30.6)	6 (27.3)	53 (31.0)	
	EDH	21 (10.9)	2 (9.1)	19 (11.1)	
	SAH	31 (16.1)	1 (4.5)	30 (17.5)	
Dominant side	Right	111 (57.5)	13 (59.1)	98 (57.3)	0.874
	Left	82 (42.5)	9 (40.9)	73 (42.7)	
Thickness of EDH or SDH (mm)	>5	64 (33.2)	16 (72.7)	48 (28.1)	<0.001 ⁺
	>0 and ≤5	66 (34.2)	4 (18.2)	62 (36.3)	
	0	63 (32.6)	2 (9.1)	61 (35.7)	
Volume of ICH (cc)	>10	10 (5.2)	2 (9.1)	8 (4.7)	0.361
	>0 and ≤10	70 (36.3)	10 (45.5)	60 (35.1)	
	0	113 (58.5)	0 (0.0)	113 (66.1)	
Midline shift (mm)	>5	10 (5.2)	6 (27.3)	4 (2.3)	<0.001 ^{*,†}
	>0 and ≤5	30 (15.5)	7 (31.8)	23 (13.5)	
	0	153 (79.3)	9 (40.9)	144 (84.2)	
Skull fracture	Yes	57 (29.5)	7 (31.8)	50 (29.2)	0.803
	No	136 (70.5)	15 (68.2)	121 (70.8)	
Compression of basal cisterns	Yes	10 (5.2)	9 (40.9)	1 (0.6)	<0.001 ^{*,†}
	No	183 (94.8)	13 (59.1)	170 (99.4)	

CT: computed tomography; GCS: Glasgow Coma Scale; WBC: white blood cell; PT: prothrombin time; INR: international normalized ratio; aPTT: activated partial thromboplastin time; SDH: subdural hematoma; ICH: intracerebral hemorrhage; EDH: epidural hematoma; SAH: subarachnoid hemorrhage; IVH: intraventricular hemorrhage.

The data is presented as number (%).

*p-value by Fisher's exact test. †p<0.05.

midline shift, compression of basal cistern were statistically related to increment of frequency of aggravated patients. Whereas, the age 65 or more, past medical history (antiplatelet agent, anticoagulation, hypertension, diabetes, chronic kidney disease, chronic liver disease, solid cancer, hematologic disease), initial vital signs (SBP ≥ 140 mmHg, PR ≥ 100 /min, RR ≥ 20 /min, BT $\geq 37.5^\circ\text{C}$), PC (groups: below 100, 100 or below 150, 150 or more $10^9/\text{L}$), PT INR over 1.2 caused no significant differences. In addition, the dominant lesion type (groups: SDH, SAH, ICH, EDH, intraventricular hemorrhage [IVH]), left side dominant lesion, presence of EDH or ICH or IVH, volume of ICH (groups: 0, 10 or below, over 10 cc) and skull fractures in the first CT scan were not statistically increased frequency of deterioration.

3. Mean Comparison of Admission Characteristics between Deteriorated and Non-deteriorated Groups

The comparison of mean value of continuous variables between 2 groups is described in Table 2. The neurologically non-deteriorated group showed lower age ($p=0.025$), higher initial GCS ($p=0.001$), lower WBC count ($p<0.004$), higher Hb level ($p=0.006$), lower PT INR ($p<0.001$), less thickness of EDH or SDH ($p<0.001$), less midline shift ($p<0.001$) compared to the mean values of deteriorated group. The SBP, PR, RR, BT, PC, aPTT, first CT time, and volume of ICH were not statistically different between 2 groups.

DISCUSSION

A mild TBI is a common injury that clinicians encounter

very often in the ER¹⁾. A 6% to 12% of them shows intracranial abnormality and they are called complicated mild TBI^(6,24). However, according to the previous reports, only 0.13% to 0.3% of mild TBI needs neurosurgical interventions^(3,4,7,14,16). In a systematic review by Stippler et al.⁽²⁷⁾, additional brain CT taken after the neurological deterioration (11/1594, 0.7%) led to more frequent neurosurgical intervention than routine follow up CT scanning (24/56, 42.9%). Therefore, patients' neurological status mainly affects the treatment strategy for mild TBI. In addition, even if the patient does not have lesions requiring neurosurgical interventions, the patient may need airway management or non-surgical critical care during the neurologically deteriorated period.

We observed 193 consecutive mild TBI patients with acute ICH in the initial CT scan. The 22 patients (11.4%) showed progressive neurological aggravation, defined as decline of GCS motor score in this study, in their first treatment week. According to Stippler et al.⁽²⁷⁾, systematic review of 19 previous publications, only 56 of 1,630 patients (3.4%) showed neurological decline which was quite lower than the frequency of this study. This is probably due to the reason that we included patients with acute intracranial hemorrhage and excluded cases only with skull fractures or pneumocephalus without bleeding.

The risk factors, according to the literatures, for clinical deterioration after mild TBI includes low initial GCS, coagulopathy, a skull fracture crossing a major sinus or the middle meningeal artery and age over 65^(2,5,8,9,28). According to the frequency analysis of this study, male sex, WBC over $10.0 \times 10^9/\text{L}$, Hb less than 12 g/dL, aPTT over 40 sec, presence of SDH or SAH, larger thickness of EDH or SDH, more midline

Table 2. Mean comparison between deteriorated and non-deteriorated groups

Admission characteristics	All patients (n=193)	Non-deteriorated (n=171)	Deteriorated (n=22)	Statistics	p-value
Age (year)	64.89	63.94	72.23	Wilcoxon	0.025*
GCS score	14.53	14.59	14.05	Wilcoxon	0.001*
Systolic blood pressure (mmHg)	141.30	141.26	141.55	T-test	0.958
Pulse rate (per min)	81.15	80.77	84.09	Wilcoxon	0.415
Respiratory rate (per min)	18.39	18.33	18.86	Wilcoxon	0.393
Body temperature ($^\circ\text{C}$)	36.72	36.73	36.60	Wilcoxon	0.486
WBC count ($10^9/\text{L}$)	8.18	7.83	10.82	Wilcoxon	0.004*
Hemoglobin (g/dL)	12.55	12.66	11.62	T-test	0.006*
Platelet count ($10^9/\text{L}$)	232.54	228.05	267.46	T-test	0.150
PT (INR)	1.05	1.04	1.12	Wilcoxon	<0.001*
aPTT	27.86	27.49	30.73	Wilcoxon	0.119
Trauma to CT time (hour)	17.90	18.54	12.91	Wilcoxon	0.796
Thickness of EDH or SDH (mm)	4.72	4.24	8.48	Wilcoxon	<0.001*
Volume of ICH (cc)	3.02	2.89	4.00	Wilcoxon	0.138
Midline shift (mm)	0.84	0.53	3.27	Wilcoxon	<0.001*

GCS: Glasgow Coma Scale; WBC: white blood cell; PT: prothrombin time; INR: international normalized ratio; aPTT: activated partial thromboplastin time; CT: computed tomography; EDH: epidural hematoma; SDH: subdural hematoma; ICH: intracerebral hemorrhage.

* $p<0.05$.

shift, compression of basal cistern were statistically related to increment of frequency of aggravated patients (Table 1). In the mean value comparison, the neurologically non-deteriorated group showed lower age, higher initial GCS, lower WBC count, higher Hb level, lower PT INR, less volume of EDH or SDH, less midline shift compared to the mean values of deteriorated group (Table 2).

The findings of the initial CT scan significantly affected progressive deterioration of the patient in this study. Especially, the mass effect by EDH or SDH was associated with the deterioration of the patient, whereas the volume of ICH showed no significance. These results are consistent with previous literatures on CT that predicts the prognosis of trauma patients^{13,18,26,30}.

Among the initial laboratory findings, in addition to coagulopathy known from previous literature, hemoglobin and WBC count were also affected the neurologic prognosis for one week in the acute mild TBI patients^{5,8,28}. Anemia has been known to be associated with the prognosis of patients with severe TBI from previous literature, and also with poor neurological outcomes in ischemic stroke and SAH patients¹⁰. In the meantime, literatures on the relationship between clinical course and hemoglobin level of mild TBI have been difficult to find, but the results of our study showed that anemia in acute mild TBI can adversely affect early neurological outcome. This suggest that oxygen delivery may be an important factor in patients with acute mild TBI, as in patients with severe TBI. WBC counts also showed statistically significant differences in both group frequency analysis and mean comparison. However, despite the statistically significant differences in mean Hb between the two groups, it is unlikely that there would be an enough difference (12.66-11.62 g/dL) to be applied to clinical practice.

The post-traumatic leukocytosis is known to be caused by increased catabolic hormones and cytokines, and eventually, increased leukocytes cause cerebral damage by occlusion and rupture of microvessels after WBC adherence to endothelium and aggregation to each other^{19,20}. In addition, they secrete cytotoxic mediators that causes additional brain damage¹⁹. The result of this study shows that these mechanisms can be applied to patients with acute mild TBI with intracranial hemorrhage.

The initial vital signs, unlike other variables, did not show any statistically significant influence in both analysis. Managing intracranial pressure (ICP) and maintaining the adequate cerebral perfusion pressure (CPP) are essential in treating brain injury and determining the optimal level of ICP and CPP is a very active research topic in severe TBI management in recent decades²⁰. In addition, what is the proper body temperature and how to maintain it, is also an important issue for ICP control. However, SBP, PR, RR, and BT do not seem to affect the early outcome in acute mild TBI patients.

This study has several limitations. It is a retrospective analysis of single center with small number of patients and the long-

term outcome is not included. In addition, only decline of GCS motor score was considered as symptomatic aggravation, whereas focal neurologic deficits such as motor weakness and speech disturbance were not investigated.

CONCLUSION

In our study, progressive mental deterioration of mild TBI patients with acute intracranial hemorrhage was not rare (11.4%). The mass effect of EDH or SDH in the initial CT scan and leukocytosis, anemia as well as coagulopathy in the laboratory tests showed to have effect on symptomatic aggravation. The vital signs such as SBP and BT, considered to be important in managing severe TBI, showed no significance on early outcome in acute mild TBI patients. However, even though there are factors showing statistically significance in this study, it is difficult to say that it has large enough differences, especially the Hb, to apply them in real clinical practice. Additional multicenter, randomized, prospective studies with larger case series are needed in the future.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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