Risk of Intracranial Hemorrhage and Short-Term Outcome in Patients with Minor Head Injury

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■ OBJECTIVE: **To examine the occurrence of traumatic intracranial hemorrhage (tICH) and outcome in patients with minor head injury and assess the probable risk factors.**

■ METHODS: **Patients with minor head injury who visited our hospital from January 2015 to July 2017 were registered consecutively, and enrolled patients were aged ≥18 years, visited within 24 hours of the injury, and had a Glasgow Coma Scale score of 15 at outpatient clinic or before the injury.**

■ RESULTS: **Of the 1122 enrolled patients, 55 (4.9%) had tICH. An antiplatelet agent was administered in 114 patients, an anticoagulant agent was administered in 49 patients, and none of them were administered in 948 patients. A multivariate analysis of tICH identified it as a risk factor, showing significant difference between antiplatelet medication (P = 0.0312), fall from stairs (P = 0.0057), traffic accident (P = 0.0117), neurologic symptoms (P = 0.0091), and modified Rankin Scale (mRS) score before trauma (P < 0.0001). We also analyzed association of enlargement of tICH with different parameters and only anticoagulant medication indicated an increased risk (P = 0.0005). Thirty patients (2.6%) were dependent or died at discharge (mRS 3–6). The mRS score before trauma (P < 0.0001), tICH (P < 0.0001), spinal injury (P < 0.0001), and enlargement of intracranial hemorrhage (P = 0.0008) indicated an increased probability of morbidity (mRS 3–6) in multivariate analysis.**

■ CONCLUSIONS: **Antiplatelet and anticoagulant medications were risk factor for tICH and enlargement of tICH in patients with minor head injury, respectively. A pretrauma condition of disability/dependence is an important risk factor for tICH and outcome.**

INTRODUCTION

Patients with minor head injury, a condition frequently encountered in routine practice, besides neurosurgery, accounts for >90% of all head injuries.[1] Most patients with minor head injury present no sequelae and have good prognosis; however, it may become severe at a certain rate. In recent years, instances of neurotrauma in the elderly have been increasing rapidly[2] because the proportion of aged people (over 65 years) are not only in developed countries but in developing countries.

In Japan, the prevalence rate of atrial fibrillation in patients in their early 60s is considered to be 1%, and 3% in those aged 80 years and older,[3] and furthermore, a future increase in anticoagulant medication use is expected in the aging society. Additionally, many patients consume antiplatelet agents for coronary and cerebrovascular events.

In this study, we examined the possible risk factors for traumatic intracranial hemorrhage (tICH) and outcome in patients with minor head injury.

METHODS

This study was approved by our institutional ethics committee (No. 4629R). Between January 2015 and July 2017, we consecutively enrolled 1122 patients with minor head trauma, aged ≥18 years, who visited our outpatient neurosurgery or emergency

Key words
- Anticoagulant
- Antiplatelet
- Elderly
- Minor head injury
- Modified Rankin Scale

Abbreviations and Acronyms
ASDH: Acute subdural hematoma
CT: Computed tomography
DOAC: Direct oral anticoagulation
GCS: Glasgow Coma Scale
ICH: Intracranial hemorrhage
mRS: Modified Rankin Scale
tICH: Traumatic intracranial hemorrhage

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Table 1. Clinical Characteristics of the Study Population (n = 1122) and the Association of Traumatic Intracranial Hemorrhage in Minor Head Injury with Different Parameters in the Univariate Analysis

Parameter	All Patients	No ICH	ICH	Hazard Ratio	95% Confidence Interval	*P* Value
No. (female)	1122 (531)	1067 (506)	55 (25)	1.082	0.628—1.865	0.7756
Age, years (range)	64.6 (18—102)	64.2 (18—102)	73.7 (30—98)			
Over 70	562 (50.1)	527 (49.4)	35 (63.6)	1.793	1.021—3.146	0.0393
Medications (%)						
Antiplatelet medication	125 (11.1)	112 (10.5)	13 (23.6)	2.639	1.374—5.066	0.0025
Anticoagulant medication	60 (5.3)	58 (5.4)	2 (3.6)	0.656	0.156—2.760	0.5630
Trauma mechanism (%)						
Fall on the ground	754 (67.2)	716 (67.1)	38 (69.1)	1.095	0.609—1.968	0.7596
Fall from stairs	95 (8.4)	85 (8.0)	10 (17.2)	2.567	1.249—5.275	0.0080
Traffic accident	80 (7.1)	80 (7.5)	0			0.0351
Sports	14 (1.2)	14 (1.3)	0			0.3926
Traumatic scalp wound (%)	816 (72.7)	772 (72.4)	44 (80.0)	1.528	0.778—2.999	0.2143
Alcohol intake (%)	255 (22.7)	242 (22.7)	13 (23.6)	1.055	0.557—1.997	0.8690
Hemorrhagic comorbidity (%)*	25 (2.2)	21 (2.0)	4 (7.3)	3.906	1.293—11.801	0.0093
Neurologic symptoms (%)†	40 (3.6)	34 (3.2)	6 (10.9)	3.720	1.491—9.279	0.0026
mRS score 2, 3, 4 before trauma (%)	21 (1.9)	7 (0.7)	14 (25.5)	51.707	19.809—134.965	<0.0001

ICH, intracranial hemorrhage; mRS, modified Rankin Scale.
*Self-reported from patients, for example, blood disorder, liver cirrhosis, and hemodialysis.
†Complaints such as headache, nausea, and dizziness.

departments within 24 hours of the injury, and had a Glasgow Coma Scale (GCS) score of 15 at outpatient clinic or before the injury. We filled out the head injury sheet for all patients. The entries included injury date, sex, age, use of antiplatelet and anticoagulant medications, trauma mechanism, traumatic scar, alcohol intake, hemorrhagic comorbidity, neurologic symptoms, condition before trauma, and imaging. Neurosurgeons were involved in the diagnosis and treatment of all cases. We examined whether the entries on the head trauma sheet could be risk factors for tICH, and moreover, examined the factors for hemorrhage enlargement.

All patients with tICH were admitted to the hospital and blood was collected. Corrections were made to patients with prolonged international normalized ratio to eventually achieve an international normalized ratio of 1.5, and blood pressure was controlled to achieve a systolic blood pressure of 150 mm Hg or less within 24 hours of admission. Follow-up computed tomography (CT) was performed the day following hospitalization if the consciousness level did not worsen. All antiplatelet and anticoagulant medications (warfarin/direct oral anticoagulation [DOAC]) were discontinued temporarily in patients with tICH, and subsequently resumed. We did not use either reverse agents or blood products in the management.

Data collected prospectively were analyzed. For statistical analysis, logistic regression was used for univariate analysis, and the odds ratios and 95% confidence intervals for each variable were estimated. We also selected risk factors by multiple logistic regression analysis using the variable reduction method. All statistical analyses were performed with JUMP 14 (SAS Institute Inc., Cary, North Carolina, USA).

RESULTS

Patient Background

Of the 1122 patients (Table 1), 591 were men and 531 were women, and aged between 18 and 102 years (average age, 64.6 years). Age-based classification (Figure 1) showed that nearly half of the 1122 patients were elderly people (251 [22.3%] in their 70s and 257 [22.9%] in their 80s). The number of patients with antiplatelet and anticoagulant medications comprised 174 (15.5%), consisting of 114 using antiplatelet agents, 49 using anticoagulant agents (33 using warfarin, 16 using DOAC), and 11 using combined antiplatelet and anticoagulant agents. Age-based classification (Figure 2) indicated that 14.3% of the patients in their 60s, 19.5% in their 70s, 35.0% in their 80s, and 27.7% in their 90s consumed antiplatelet or/and anticoagulant medications.

The most frequent head trauma mechanism was falling on the ground, accounting for 754 patients (67.2%), followed by fall from stairs in 95 (8.4%), and traffic accident in 80 (7.1%). There were 255 patients (22.7%) with alcohol intake, and 816 (72.7%) had redness, subcutaneous hematoma, or injury on the scalp. Twenty-five patients (2.2%) had a hemorrhagic comorbidity,

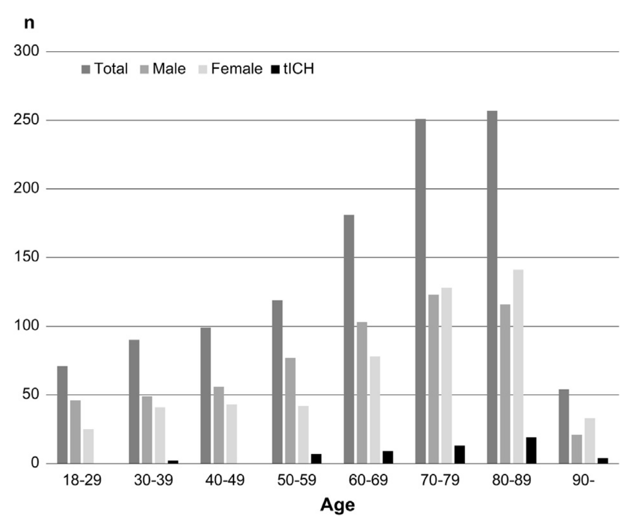

Figure 1. Age, sex distribution, and incidence of traumatic intracranial hemorrhage (tICH) of 1122 patients with minor head injury visited to authors' hospital between January 2015 and July 2017.

such as blood disease, liver cirrhosis, and dialysis induction, at the time of hospital visit. Forty patients (3.5%) had neurologic symptoms, such as headache, dizziness, and nausea, at the time of hospital visit.

Head and/or spinal CT examinations were performed in 1047 patients (93.3%); 60 (5.3%) of which were traumatic lesions, including 55 (4.9%) of tICH, 13 (2.2%) of skull fractures, and 5 (0.5%) of spinal fractures and spinal cord injuries. Further categorization of the tICH patients (Figure 3) indicated 5 with acute epidural hematoma, 23 with acute subdural hematoma (ASDH), 7 with ASDH and brain contusion, and 20 with traumatic subarachnoid hemorrhage or brain contusion. Among the 60 patients with traumatic lesions, surgical repair was done in 11 patients: 2 with acute epidural hematoma, 3 with ASDH, 1 with ASDH and brain contusion, 1 with traumatic subarachnoid hemorrhage and brain contusion, and 4 with spinal fracture and spinal cord injury.

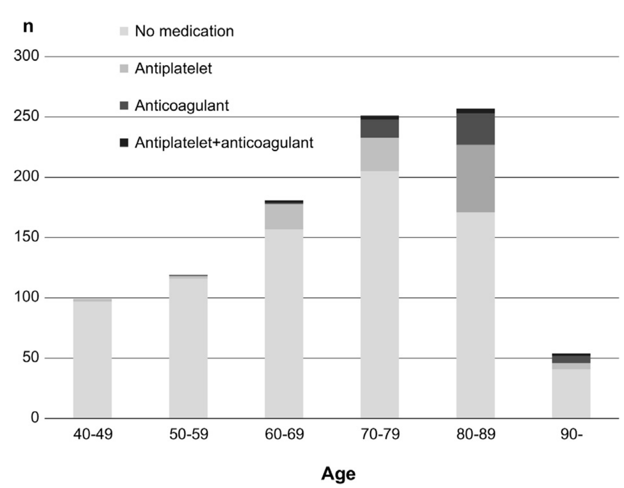

Figure 2. Age and antiplatelet and anticoagulant medication in patients aged over 40 years with minor head injury in Figure 1.

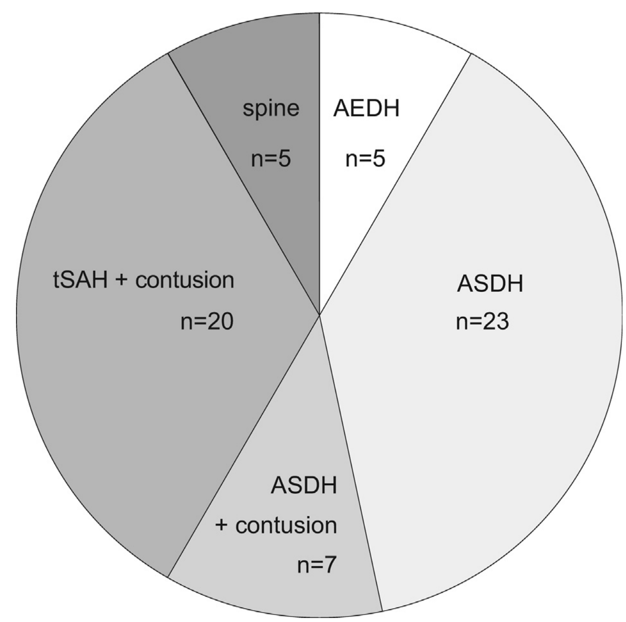

Figure 3. Head and spinal computed tomography findings of traumatic lesions in 60 patients with minor head injury. AEDH, acute epidural hematoma; ASDH, acute subdural hematoma; tSAH, traumatic subarachnoid hemorrhage.

Intracranial Hemorrhage

Among 55 patients with tICH (Table 1), 13 patients were using antiplatelet agents, 2 were using anticoagulant medication, and

Table 2. Association of Traumatic Intracranial Hemorrhage with Different Parameters in 1122 Patients with Minor Head Injury in the Multivariate Analysis

Parameter	Hazard Ratio	95% Confidence Interval	*P* Value
Age	1.685	0.882—3.219	0.1089
Antiplatelet medication	2.355	1.120—4.950	0.0312
Fall from stairs	3.353	1.527—7.361	0.0057
Traffic accident			0.0117
Hemorrhagic comorbidity	3.957	1.131—13.838	0.0566
Neurologic symptoms	4.554	1.664—12.462	0.0091
mRS score 2, 3, 4 before trauma	71.657	24.824—206.842	<0.0001

mRS, modified Rankin Scale.

Table 3. Association of Enlargement of Traumatic Intracranial Hemorrhage with Different Parameters in Patients with Minor Head Injury in the Univariate Analysis

Parameter	All ICH Patients	No Enlargement	Enlargement	Hazard Ratio	95% Confidence Interval	*P* Value
No. (female)	55 (27)	47 (25)	8 (2)	3.409	0.622—18.657	0.1404
Age, years (range)	73.7 (30—98)	73.8 (35—98)	73.0 (30—92)			
Over 70	37 (67.3)	31 (66.0)	6 (75.0)	1.548	0.279—8.563	0.6143
Medications (%)						
Antiplatelet medication	14 (25.5)	13 (27.7)	1 (12.5)	0.373	0.041—3.340	0.3629
Anticoagulant medication	2 (3.6)	0	2 (25.0)			0.0005
Trauma mechanism (%)						
Fall on the ground	38 (69.1)	32 (68.1)	6 (75.0)	1.406	0.253—7.804	0.6956
Fall from stairs	10 (17.2)	10 (21.3)	0			0.1492
Traffic accident	0	0	0			
Sports	0	0	0			
Traumatic scalp wound (%)	45 (81.8)	38 (80.9)	7 (87.5)	1.657	0.180—15.229	0.6522
Alcohol intake (%)	14 (25.5)	12 (25.5)	2 (25.0)	0.972	0.172—5.480	0.9745
Hemorrhagic comorbidity (%)*	4 (7.3)	4 (8.5)	0			0.3915
Neurologic symptoms (%)†	6 (10.9)	5 (10.6)	1 (12.5)	1.2	0.121—11.865	0.8759
mRS score 2, 3, 4 before trauma (%)	14 (25.5)	13 (27.7)	1 (12.5)	0.373	0.041—3.340	0.3629

ICH, intracranial hemorrhage; mRS, modified Rankin Scale.
*Self-reported from patients, for example, blood disorder, liver cirrhosis, and hemodialysis.
†Complaints such as headache, nausea, and dizziness.

40 were without either of them. Univariate analysis was performed to assess the risk factors for tICH (Table 1). No significant difference was observed among the sexes, whereas an age cutoff rate of 70 years demonstrated a significant difference, and the incidence rate of tICH was high among the elderly ($P = 0.0393$). The incidence of tICH was significantly elevated among users of an antiplatelet agent ($P = 0.0025$); however, an anticoagulant use was not identified as a risk factor. Fall from stairs and traffic accident were risk factors for tICH with significant difference observed among the different trauma mechanisms ($P = 0.0080$ and $P = 0.0351$, respectively). Additionally, the incidence of tICH was significantly higher in patients with hemorrhagic comorbidity ($P = 0.0093$) and neurologic symptoms ($P = 0.0026$). The modified Rankin Scale (mRS) score before trauma as also highly related to the incidence of tICH ($P < 0.0001$). The results of the multivariate analysis are presented in Table 2. Antiplatelet agent ($P = 0.0312$), fall from stairs ($P = 0.0057$), traffic accident ($P = 0.0117$), neurologic symptoms ($P = 0.0091$), and mRS score before trauma ($P < 0.0001$) indicated an increased probability of tICH, whereas age and hemorrhagic comorbidity did not.

We also analyzed association of enlargement of tICH with different parameters and only anticoagulant medication indicated an increased risk ($P = 0.0005$; Table 3).

Short-Term Outcomes of Patients with Minor Head Injury

Among 1122 patients with minor head injury, 30 (2.6%) were dependent or died at discharge (mRS 3—6; Table 4). Although 12 patients with mRS score 3 and 1 patient with mRS score 4 before trauma were automatically allocated to this group, 6 patients deteriorated. The mRS score before trauma ($P < 0.0001$), tICH ($P < 0.0001$), skull fracture ($P < 0.0001$), spinal injury ($P < 0.0001$), and enlargement of intracranial hemorrhage (ICH; $P < 0.0001$) were related to morbidity (mRS 3—6) in the univariate analysis. The results of the multivariate analysis are presented in Table 5. The mRS score before trauma ($P < 0.0001$), tICH ($P < 0.0001$), spinal injury ($P < 0.0001$), and enlargement of ICH ($P = 0.0008$) indicated an increased probability of morbidity (mRS 3—6).

Although the overall mortality rate was 2/1125 (0.18%), the mortality rate in hospitalized patients was 2/83 (2.4%). There was no death in patients without tICH. The causes of death were intracranial lesions in 1 patient and aspiration pneumonia in 1 patient; their ages were 92 and 74 years, respectively.

DISCUSSION

Of the 1122 minor traumatic head injury patients included, 565 (50.2%) were aged 70 years and older, indicating the high prevalence of elderly individuals with head injuries. It has been known that the frequency of traumatic brain injury by age has 2 peaks: ages 15—29 and 65—79 years. Recently, it has a single peak in the elderly, resulting from rapid changes in population structure.[2] Age as a risk factor for tICH has been well studied in different populations and has been shown that age is associated with tICH.[4-6] Minor traumatic

Table 4. Association of Modified Rankin Scale Score at Discharge with Different Parameters in 1122 Patients with Minor Head Injury in the Univariate Analysis

Parameter	All Patients	mRS 0, 1, 2	mRS 3, 4, 5, 6	Hazard Ratio	95% Confidence Interval	*P* Value
No. (female)	1122 (531)	1092 (517)	30 (14)	1.027	0.496—2.126	0.9415
Age, years (range)	64.6 (18—102)	64.5 (18—102)	69.3 (35—90)			
Over 70	562 (50.1)	546 (50.0)	16 (53.3)	1.142	0.552—2.364	0.7187
Medication (%)						
Antiplatelet medication	125 (11.1)	121 (11.1)	4 (13.3)	1.234	0.423—3.597	0.6988
Anticoagulant medication	60 (5.3)	58 (5.3)	2 (6.7)	1.273	0.296—5.476	0.7448
Trauma mechanism (%)						
Fall on the ground	754 (67.2)	732 (67.0)	22 (73.3)	1.352	0.596—3.067	0.4684
Fall from stairs	95 (8.4)	90 (8.2)	5 (16.7)	2.226	0.832—5.957	0.1020
Traffic accident	80 (7.1)	79 (7.2)	1 (3.3)	0.442	0.059—3.288	0.4127
Sports	14 (1.2)	14 (1.3)	0			0.5326
Traumatic scalp wound (%)	816 (72.7)	792 (72.5)	24 (80.0)	1.515	0.613—3.743	0.3646
Alcohol intake (%)	255 (22.7)	248 (22.7)	7 (23.3)	1.035	0.439—2.442	0.9360
Hemorrhagic comorbidity (%)*	25 (2.2)	25 (2.3)	0			0.4020
Neurologic symptoms (%)†	40 (3.6)	37 (3.4)	3 (12.5)	3.168	0.919—10.915	0.0540
mRS score 2, 3, 4 before trauma (%)	21 (1.9)	6 (0.5)	15 (50.0)	181	61.764—530.415	<0.0001
Radiologic examination (%)	1047 (93.3)	1023 (91.1)	24 (80.0)			
Traumatic ICH	55 (4.9)	32 (2.9)	23 (76.7)	108.839	43.538—272.080	<0.0001
Skull fracture	13 (1.2)	9 (0.8)	4 (16.7)	18.512	5.355—63.996	<0.0001
Spinal injury	5 (0.5)	2 (0.2)	3 (10.0)	60.555	9.718—377.302	<0.0001
Enlargement of ICH	8 (0.7)	2 (0.2)	6 (20.0)	136.250	26.150—709.893	<0.0001

ICH, intracranial hemorrhage; mRS, modified Rankin Scale.
*Self-reported from patients, for example, blood disorder, liver cirrhosis, and hemodialysis.
†Complaints such as headache, nausea, and dizziness.

injury is also associated with increased risk of death and long-term poor outcome in elderly patients. Cerebrovascular atherosclerosis during aging could increase the risk of injury and induce a secondary insult.[6] This is reflected in clinical guidelines and decision rules regarding the need for CT in patients with minor head injury. The New Orleans criteria as a risk factor for tICH define age >60 years and Canadian CT Head Rule age ≥65 years.[7,8]

Table 5. Association of Modified Rankin Scale Score at Discharge with Different Parameters in 1122 Patients with Minor Head Injury in the Multivariate Analysis

Parameter	Hazard Ratio	95% Confidence Interval	*P* Value
mRS score 2, 3, 4 before trauma	176.081	30.784—1007.145	<0.0001
Traumatic ICH	80.992	18.931—346.510	<0.0001
Skull fracture	0.203	0.024—1.669	0.1248
Spinal injury	962.424	96.676—9581.021	<0.0001
Enlargement of ICH	24.757	3.033—202.076	0.0008

ICH, intracranial hemorrhage; mRS, modified Rankin Scale.

However, our study did not show elderly itself is an independent risk for tICH and poor outcome after minor head injury. Figure 2 shows elderly patients tend to take antiplatelet and anticoagulant agents more than younger patients. The multivariate analysis of our data demonstrated that not age but pretrauma condition was highly related to occurrence of tICH (hazard ratio = 71.657, $P < 0.0001$) and outcome. Sauter et al.[9] and Hamden et al.[10] favor our results. No association was found between age and intracranial bleeding in patients with mild traumatic brain injury and oral anticoagulation. Elderly fall patients who are at their baseline mental status have a low incidence of tICH. To date, degree of disability/dependence, as well as age have not been reported as a risk factor for tICH in minor head trauma. We should consider that not only age but pretrauma condition of disability/dependence is an important risk factor for tICH.

We enrolled patients with minor head trauma, aged ≥18 years, and who had a GCS score of 15 at outpatient clinic or before the injury. Among risk factors for tICH, neurologic symptoms are significantly related (hazard ratio = 4.554, $P = 0.0091$). The results obtained in this study are consistent with the known risk factors. All patients with positive CT scans reported to have at least 1 of 7 findings: headache, vomiting, age over 60 years, drug or alcohol intoxication, deficits in short-term memory, physical evidence of trauma above the clavicles, and seizure in 1429 patients with minor head injury.[7] Canadian CT Head Rule is required for patients with minor head injuries (GCS score 13–15) with any one of the following: GCS score <15 at 2 hours after injury; suspected open or depressed skull fracture; any sign of basal skull fracture; vomiting ≥2 episodes; age ≥65 years; amnesia before impact >30 minutes; dangerous mechanism, including fall from >5 stairs.[8] The European Federation for Neurological Societies Mild Head Trauma Guidelines includes coagulation disorders as one of the risk factors for intracranial complications after mild traumatic brain injury.[11]

Antiplatelet and anticoagulant medications were not described in these guidelines for CT rules for patients with minor head injury, probably because whether these drugs are related to risk for tICH or outcome is controversial. Recent meta-analysis revealed that antiplatelet therapy in patients with minor head injury is associated with increased risk of tICH. This association is most relevant in patients with mild traumatic brain injury.[12] A prospective, observational study of 1064 patients with blunt head trauma and preinjury warfarin or clopidogrel use at 2 trauma centers and 4 community hospitals demonstrated that patients receiving clopidogrel have a significantly higher prevalence of immediate tICH compared with patients receiving warfarin.[13] Delayed tICH is rare but occurred only in patients receiving warfarin. Beynon et al.[14] reported that rivaroxaban, one of the DOAC medications, may exacerbate tICH in patients with mild traumatic brain injury. It is agreeable that patients with antiplatelet agents tend to be associated with higher risk of tICH. On the contrary, 3 retrospective studies reported negative results for anticoagulants.[15-17] In our findings, antiplatelet and anticoagulant medications were related to occurrence of tICH and enlargement of tICH, respectively, although both were not directly associated with outcome.

Our results may be supported by the mechanism of hemostasis following injury. Following the rupture of blood vessels, the platelet membrane proteins and intravascular subcutaneous tissue are bound via the von Willebrand factor, and the primary aggregation results in primary hemostasis. Thereafter phosphodiesterase and thromboxane A2 are released, resulting in further aggregation of platelets, and continuous stimulation via the adenosine diphosphate receptor, which stabilizes the platelet aggregate, leading to secondary aggregation. The coagulation cascade proceeds by the activation of coagulation factors to form a fibrin thrombus, achieving complete secondary hemostasis. Antiplatelet agents are classified based on their action on thromboxane and prostaglandin (such as aspirin and ethyl icosapentate), and those targeting cyclic adenosine monophosphate and Ca ions concentration (such as clopidogrel and cilostazol), which are involved in the primary hemostasis. It is to inhibit the predisposition. Additionally, the von Willebrand factor acts on the vitamin K-dependent coagulation factor of the coagulation cascade, and DOACs directly act on the factor Xa or antithrombin, which are involved in the secondary hemostasis.[18,19] Therefore following the rupture of blood vessels due to head injury, the patients taking antiplatelet agents (whose primary hemostasis cascade is inhibited) are the primary candidates prone to hemorrhage, and those on anticoagulants (whose secondary hemostasis cascade is inhibited) present further hemorrhaging. It has been suggested that patients on anticoagulant medicine exhibit a tendency for repeated hemorrhage.[13,14,20]

We showed that mRS score before trauma, tICH, spinal injury, and enlargement of ICH indicated an increased probability of morbidity (mRS 3–6) at discharge. Preinjury antiplatelet and anticoagulant medications in patients with traumatic brain injury or trauma have been reported to lead to increased risk for disability.[20-22] Our data did not prove that they are directly related to short-term functional outcome in patients with mild head injury (GCS score = 15). This is probably because the impact of injury may not be severe, the number of patients with tICH may not be large, and tICH may be treated successfully. However, we should always consider that antiplatelet and anticoagulant medications are risks for tICH and enlargement of tICH, which may be related to functional outcome.[23]

Three of 5 patients with spine injury became dependent status at discharge, although the number of spine injury was very small after minor head injury. It has been reported that patients with degenerative diseases of the cervical spine sometimes present with acute spinal cord injury caused by minor trauma. Spinal injury also cannot be ignored after mild head injury.[24]

CONCLUSIONS

Antiplatelet and anticoagulant medications were risk factor for tICH and enlargement of tICH in patients with minor head injury, respectively. A pretrauma condition of disability/dependence is an important risk factor of tICH and outcome.

CRediT AUTHORSHIP CONTRIBUTION STATEMENT

Chika Yamada: Data curation, Formal analysis, Writing - original draft, Writing - review & editing. **Shinji Hagiwara:** Writing - review & editing. **Hidenori Ohbuchi:** Writing - review & editing. **Hidetoshi Kasuya:** Supervision, Writing - original draft.

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