Heliyon 10 (2024) e25193

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Research article

The current status of reversal therapy in Japan for elderly patients with head injury treated with antithrombotic agents: A prospective multicenter observational study

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ARTICLE INFO

Keywords:
Traumatic brain injury
Reversal therapy
Antithrombotic agents
Acute exacerbation

ABSTRACT

Background: Acute exacerbation of head injury in elderly patients due to use of antithrombotic agents has become a concern in countries with aging populations. Reversal agents are recommended for treatment, but its usage is unclear. Therefore, we conducted a prospective observational study in this patient population to monitor usage of reversal therapy.

Methods: The subjects were 721 elderly patients aged ≥65 years old who were hospitalized in 15 centers from December 2019 to May 2021. Patients were divided into groups who did not receive antithrombotic agents (Group A), who received antithrombotic agents, but did not receive reversal therapy (Group B), and were treated with antithrombotic agents and reversal therapy

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https://doi.org/10.1016/j.heliyon.2024.e25193
Received 9 June 2023; Received in revised form 18 December 2023; Accepted 22 January 2024
Available online 24 January 2024

(Group C). Age, gender, mechanism of injury, neurologic and imaging findings on admission, clinical course after admission and surgery, outcomes and complications were compared among these groups. Time from injury to reversal therapy was examined based on outcomes to investigate trends in the timing of administration of the reversal agent.

Results: Acute exacerbation during the clinical course occurred in 9.8 %, 15.8 % and 31.0 % of cases in Groups A, B and C, respectively, and differed significantly among the groups. On head CT, the incidences of hematoma were 35.7 %, 36.5 % and 60.4 %, respectively, with this incidence being significantly higher in Group C; and the respective rates of craniotomy were 18.8 %, 14.0 % and 50.9 %, again with this rate being significantly higher in Group C. The good outcome and mortality rates were 57.1 %, 52.5 % and 35.8 %, and 14.5 %, 18.0 % and 24.5 %, respectively, and both were poorest in Group C. Times from injury to treatment with a reversal agent were significantly shorter in patients without compared to those with acute exacerbation (405.9 vs. 880.8 min) and in patients with favorable outcomes compared to those with unfavorable outcomes (261.9 vs. 543.4 min).

Conclusion: Similarly to previous studies, the incidence of acute exacerbation was increased by use of antithrombotic agents. These results suggest that patients in Japan who require hematoma evacuation due to symptom exacerbation tend to be treated with reversal agents. Although it is difficult to assess the efficacy of reversal therapy from this study, earlier treatment with reversal agents before the occurrence of acute exacerbation may be useful to improve outcomes.

1. Introduction

Japan has the highest aging population worldwide and there is a major need to cope with changes in the structure of society [1], including addressing medical needs. The Japan Neurotrauma Data Bank has reported that more than half of patients with severe head injury are elderly; that is, aged ≥65 years old. This indicates that neurosurgeons will increasingly have to treat elderly patients and establish therapeutic strategies for these patients. Japan is facing a super-aging society and should be a world leader in this area. The characteristics of head injury in elderly people include acute subdural hematoma caused by fall [2,3], no symptoms early after injury, but symptom exacerbation with time [4], and wide use of antithrombotic agents [5]. In a previous study [6] in this patient population, we concluded that treatment including reversal agents for antithrombotic agents was required because patients who took antithrombotic agents showed significantly greater deterioration compared to those who did not.

Antithrombotic agents may be a risk for traumatic/non-traumatic intracranial hemorrhage (ICH) [7,8], and ICH that develops in patients given these agents requires an appropriate therapeutic strategy, including discontinuation and resumption of the antithrombotic agents, and use of reversal therapy [9]. The Neurocritical Care Society guidelines for patients with ICH related to antithrombotic agents recommend discontinuation of these agents and initiation of reversal therapy [10], but there is no data showing the effects of this approach. There are some studies on the efficacy of reversal therapy for ICH associated with anticoagulant therapy [11,12], but reversal therapy has been suggested to be ineffective in patients with severe head injury [13].

With this background, we conducted a prospective multicenter observational study of elderly patients with head injury who were given antithrombotic agents in Japan. Here, the content, status of use of reversal therapy for antithrombotic agents are examined.

2. Methods

A prospective observational study was performed in patients with traumatic brain injury (TBI) aged ≥65 years old who required hospitalization. Data on TBI were obtained from 15 collaborating clinical centers: Iwate Medical University, Sendai City Hospital, Tsuchiura Kyodo General Hospital, Chiba Emergency Medical Center, Teikyo University Hospital, Nippon Medical School Hospital, Nihon University Hospital, National Disaster Medical Center, St. Marianna University Hospital, Tokyo Medical and Dental University Hospital, Saiseikai Shiga Hospital, Hyogo Prefectural Kakogawa Medical Center, Kagawa University Hospital, Yamaguchi University Hospital, and the Japanese Red Cross Kumamoto Hospital. These participating institutions are actively involved in head injury care and follow the Japanese guidelines for the management of severe head injury and treatment [14]. The physicians at each site made judgments on the appropriate cases for reversal therapy against antithrombotic drugs according to guidelines for management of severe head injury [14]. These guidelines state that anticoagulants and antiplatelet agents should be discontinued or reversed in patients with head injury who are taking antithrombotic drugs, but that careful consideration is required based on the underlying disease in each case [14].

The study was conducted from December 2019 to May 2021 in 721 patients. Age, sex, cause of injury, Glasgow Coma Scale (GCS) on admission, pupillary abnormalities, head computed tomography (CT) findings, details of antithrombotic therapy including reversal therapy, acute exacerbation (sudden drop of GCS by ≥ 2), craniotomy, time from injury to administration of reversal therapy, and outcomes at 6 months post-injury were examined. GCS on admission was assessed by primary care physicians prior to sedation on hospital arrival. Abnormal pupils were defined as anisocoria with a left-right difference of 0.5 mm or more in pupil diameter or dilated pupils with dilated pupils of 5 mm or more on both sides and no light reflex. Head CT findings were defined as hematoma in Category V or VI using the Marshall CT score. Antithrombotic drugs included aspirin, clopidogrel, prasugrel, and cilostazol as antiplatelet drugs, and vitamin K antagonists (VKA), dabigatran, and Xa inhibitors as anticoagulants. Platelet transfusion is performed as reversal therapy

for antiplatelet drugs, and fresh frozen plasma, vitamin K, prothrombin complex concentrate, and idarucizumab are used for each anticoagulant drug. During the study period, the use of andexanet alfa was not permitted in Japan. Acute exacerbation was defined as a rapid decrease in GCS by $\geq$ 2 points.

To examine the effects of antithrombotic drugs, the subjects were classified into four groups based on antithrombotic therapy: no antithrombotic therapy, antiplatelet therapy, anticoagulant therapy, and combined antiplatelet/anticoagulant therapy. In another evaluation to examine the effects of reversal therapy, the subjects were classified into three groups: patients who did not receive antithrombotic agents (Group A) and those who were given antithrombotic agents and did not (Group B) or did (Group C) receive reversal therapy. Age, sex, fall as a cause of injury, medical history, GCS on admission, pupillary abnormalities, hematoma on head CT, reversal therapy, acute exacerbation, craniotomy, and outcomes were compared among these groups. The Glasgow Outcome Scale at 6 months post-injury was used to assess outcomes, with good recovery or moderate disability defined as a favorable outcome. Ischemic and hemorrhagic complications during hospitalization were also investigated in patients in group C, who received reversal therapy. To examine the status of the timing of administration, the time from injury to use of reversal therapy was compared in cases with and without favorable outcomes.

The statistical significance of categorical and nominal data was determined by chi-square test. Continuous data are presented as the mean $\pm$ standard deviation, and comparisons were performed with a Tukey HSD test or an unpaired *t*-test. Significance was assumed at $P < 0.05$. All statistical analyses were conducted using SPSS 20.0 (IBM, New York).

3. Results

The mean age of the 721 subjects (62.6 % male) was 79.4 $\pm$ 7.8 years (Table 1). The main causes of injury were fall (n = 392, 54.4 %) and a traffic accident (n = 147, 20.4 %) (Table 1). The GCS on admission was 11.9 $\pm$ 3.9 and the prevalence of pupillary abnormality was 11.0 % (Table 1). In head CT findings, 272 subjects (37.7 %) had hematoma with a mass effect (Table 1). Antithrombotic therapy was administered in 253 cases (35.1 %), of which 53 (20.9 %) received reversal therapy (Table 2). Acute exacerbation occurred in 84 cases (11.7 %) and 143 cases (19.8 %) underwent craniotomy (Table 1). The rate of favorable outcomes at 6 months after injury was 54.2 % and mortality was 16.2 % (Table 1).

Of the 253 subjects (35.1 %) who underwent antithrombotic therapy, 137 (19.0 %) were treated with antiplatelet therapy, 86 (11.9 %) with anticoagulant therapy, and 30 (4.2 %) with combined antiplatelet and anticoagulant therapy (Table 2). The mean ages in these respective groups were 81.2 $\pm$ 7.5, 82.2 $\pm$ 7.0 and 80.1 $\pm$ 6.9 years, and those in the first two groups were significantly higher than that of 78.3 $\pm$ 7.8 years in patients who did not receive antithrombotic therapy (untreated group) (Table 2). The rates of fall as a cause of injury were 47.0 %, 67.2 %, 62.8 % and 86.7 % in the untreated, antiplatelet, anticoagulant, and combined therapy groups, with significantly higher rates in all three treatment groups compared to the untreated group (Table 2). GCS scores on admission were 11.9 $\pm$ 3.9, 12.3 $\pm$ 3.7, 11.8 $\pm$ 4.3 and 11.9 $\pm$ 4.3 in the respective groups (Table 2). In head CT, the rates of hematoma were 35.7 %, 40.9 %, 38.4 % and 53.3 %, respectively, with no significant differences among the groups (Table 2). The rates of reversal therapy were 0 %, 4.4 %, 40.7 %, and 40.0 %, respectively. Significantly more patients taking anticoagulants received reversal therapy compared to those

Table 1
Characteristics of Patients in this Study.

Number of patients	721
Age	79.4 $\pm$ 7.8
Sex (male)	451 (62.6 %)
Mechanism of injury	
Traffic accident	147 (20.4 %)
Tumble	392 (54.4 %)
Fall	140 (19.4 %)
Other	42 (5.8 %)
Glasgow Coma Scale on admission	11.9 $\pm$ 3.9
Pupillary abnormalities	79 (11.0 %)
CT findings	
ASDH	204 (28.3 %)
Contusion/ICH	27 (3.7 %)
AEDH	41 (5.7 %)
No hematoma	449 (62.3 %)
Antithrombotic therapy	
None	468 (64.9 %)
Antiplatelet therapy	137 (19.0 %)
Anticoagulant therapy	86 (11.9 %)
Combined antiplatelet/anticoagulant therapy	30 (4.2 %)
Deterioration in the acute phase	84 (11.7 %)
Craniotomy	143 (19.8 %)
Outcome	
Favorable outcome	391 (54.2 %)
Mortality	117 (16.2 %)

The table shows CT = computed tomography; ASDH = acute subdural hematoma; ICH = intracranial hemorrhage; AEDH = acute epidural hematoma.

Table 2
Characteristics of Patients by group separated by antithrombotic agents.

Group	No antithrombotic Therapy (n = 468)	Antiplatelet Therapy (n = 137)	Anticoagulant Therapy (n = 86)	Combined antiplatelet/anticoagulant therapy (n = 30)
Age (y.o.)	78.3 ± 7.8	81.2 ± 7.5[a]	82.2 ± 7.0[a]	80.1 ± 6.9
Sex (male)	278 (59.4 %)	96 (67.0 %)	58 (67.4 %)	19 (63.3 %)
Mechanism of injury (tumble)	220 (47.0 %)	92 (67.2 %)[a]	54 (62.8 %)[a]	26 (86.7 %)[a]
Medical history				
hypertension	182 (38.9 %)[b]	90 (65.7 %)[a]	45 (52.3 %)	12 (40.0 %)
diabetes	67 (14.3 %)[b]	51 (37.2 %)[a,c]	17 (19.8 %)[b]	7 (23.3 %)
Chronic renal failure	24 (5.1 %)[b,d]	18 (13.1 %)[a]	8 (9.3 %)	8 (26.7 %)[a]
Cerebrovascular disease	26 (5.6 %)[b,c,d]	56 (40.9 %)[a,c]	16 (18.6 %)[a,b]	12 (40.0 %)[a]
Ischemic heart disease	14 (3.0 %)[b,c,d]	58 (42.3 %)[a,c,d]	8 (9.3 %)[a,b,d]	14 (46.7 %)[b,c,d]
Glasgow Coma Scale on admission	11.9 ± 3.9	12.3 ± 3.7	11.8 ± 4.3	11.9 ± 4.3
Pupillary abnormalities	45 (9.6 %)	13 (9.5 %)	17 (19.8 %)[a]	4 (13.3 %)
CT findings (hematoma)	167 (35.7 %)	56 (40.9 %)	33 (38.4 %)	16 (53.3 %)
Reversal therapy	0 (0 %)[b,c,d]	6 (4.4 %)[a,c,d]	35 (40.7 %)[a,b]	12 (40.0 %)[a,b]
Deterioration in the acute phase	41 (8.8 %)[c]	20 (14.6 %)	17 (19.8 %)[a]	6 (20.0 %)
Craniotomy	88 (18.8 %)	25 (18.2 %)	24 (27.9 %)	6 (20.0 %)
Favorable outcome	267 (57.1 %)	72 (52.6 %)	39 (45.3 %)	13 (43.3 %)
Mortality	68 (14.5 %)	21 (15.3 %)	21 (24.4 %)	7 (23.3 %)

[a] $P < 0.05$ versus No antithrombotic therapy.
[b] $P < 0.05$ versus Antiplatelet therapy.
[c] $P < 0.05$ versus Anticoagulant therapy.
[d] $P < 0.05$ versus Combined antiplatelet/anticoagulant therapy.

taking antiplatelets (Table 2). The rates of acute exacerbation were 8.8 %, 14.6 %, 19.8 % and 20.0 %, respectively, and were significantly higher in the anticoagulant groups (Table 2). There were no significant differences among the groups in the rates of craniotomy (18.8 %, 18.2 %, 27.9 %, 20.0 %), favorable outcomes (57.1 %, 52.6 %, 45.3 %, 43.3 %), and mortality (14.5 %, 15.3 %, 24.4 %, 23.3 %) (Table 2).

A total of 468 subjects did not receive antithrombotic therapy (Group A). Of the 253 treated with antithrombotic agents, 200 (Group B) received no reversal therapy and 53 (Group C) received reversal therapy (Table 3). The mean ages in the respective groups were 78.3 ± 7.8, 81.9 ± 7.3 and 79.7 ± 7.0 years, and patients in Group B were significantly older than those in Group A (Table 3). The rates of fall as a cause of injury were 47.0 %, 68.0 % and 67.9 %, respectively, and this rate was significantly lower in Group A (Table 3). The respective GCS scores on admission were 11.9 ± 3.9, 12.5 ± 3.7 and 10.5 ± 4.6, with significantly more severe injury in Group C (Table 3). This group also had the highest rate of abnormal pupils. The rates of hematoma on head CT were 35.7 %, 36.5 % and 60.4 %, and those of craniotomy were 18.8 %, 14.0 % and 50.9 %, respectively (Table 3). Both rates were significantly higher in Group C (Table 3).

The rate of antiplatelet therapy was significantly higher in Group B than in Group C, whereas that of anticoagulant therapy was significantly higher in Group C than in Group B (Table 3). The acute exacerbation rates were 9.8 %, 15.8 % and 31.0 % in Groups A, B and C, respectively, with significant differences among all groups (Table 3). The favorable outcome rates were 57.1 %, 52.5 % and 35.8 %, respectively, with a significantly lower rate in Group C (Table 3). The mortality was 14.5 %, 18.0 % and 24.5 %, respectively (Table 3). Among Group C cases that underwent reversal therapy against antithrombotic agents, 4 (7.6 %) and 1 (1.9 %) developed ischemic and hemorrhagic stroke as a complication during hospitalization.

The time from injury to administration of a reversal agent was significantly shorter in patients without acute exacerbation compared to those with acute exacerbation (405.9 ± 559.8 vs. 880.8 ± 836.3 min) (Fig. 1) and in those with a favorable outcome compared to those with an unfavorable outcome (261.9 ± 233.2 vs. 543.4 ± 652.4 min) (Fig. 2).

Table 3
Characteristics of Patients by group.

Group	Group A (n = 468)	Group B (n = 200)	Group C (n = 53)
Age (y.o.)	78.3 ± 7.8	81.9 ± 7.3 *	79.7 ± 7.0
Sex (male)	278 (59.4 %)	134 (67.0 %)	39 (73.6 %) *
Mechanism of injury (tumble)	220 (47.0 %)	136 (68.0 %) *	36 (67.9 %) *
Glasgow Coma Scale on admission	11.9 ± 3.9	12.5 ± 3.7 *	10.5 ± 4.6 *, **
Pupillary abnormalities	45 (9.6 %)	23 (11.5 %)	11 (20.8 %) *
CT findings (hematoma)	167 (35.7 %)	73 (36.5 %)	32 (60.4 %) *, **
Antiplatelet therapy	0 (0 %)	149 (74.5 %) *	18 (34.0 %) *, **
Anticoagulant therapy	0 (0 %)	69 (34.5 %) *	47 (88.7 %) *, **
Deterioration in the acute phase	46 (9.8 %)	32 (15.8 %) *	16 (31 %) *, **
Craniotomy	88 (18.8 %)	28 (14.0 %)	27 (50.9 %) *, **
Favorable outcome	267 (57.1 %)	105 (52.5 %)	19 (35.8 %) *, **
Mortality	68 (14.5 %)	36 (18 %)	13 (24.5 %)

*$P < 0.05$ versus Group A, **$P < 0.05$ versus Group B.

4. Discussion

In countries with aging populations, use of reversal therapy for antithrombotic agents is recommended as a countermeasure against head injury in elderly patients [15,16], but the clinical status of this therapy is unclear. In our previous study [6] in this patient population, only cases of severe head injury were included. In contrast, the current prospective observational study included elderly patients with mild and moderate head injury who required hospitalization and were given antithrombotic agents. Thus, the results of this study are more reflective of clinical practice compared to those in the previous study. The characteristics of the patients included a high incidence of fall as a cause of injury, many cases with moderate head injury, and hematoma in 37.7 % of subjects. Symptoms exacerbated in 11.7 % of all subjects during the clinical course, which was about half the rate in the previous study. Antithrombotic agents were given in 35.1 % of cases, which was slightly higher than the rate in the previous study, and 20.9 % of subjects given antithrombotic agents received reversal therapy, showing that use of this therapy remains limited.

A comparison of patient background depending on antithrombotic agents indicated that fall was the most common reason for injury in patients given antithrombotic agents, which is consistent with previous studies [6,17]. Our results also confirmed that antithrombotic agents can induce symptom exacerbation in patients with low-energy injury [6,17]. The incidence of symptom exacerbation in the anticoagulant group was significantly higher than that in the no treatment group, which indicates that use of anticoagulants causes exacerbation. In particular, reversal therapy for antiplatelet agents was significantly lower than that with anticoagulants (4.4 % vs. 40.7 %). These results suggest that reversal therapy is more actively performed with anticoagulants, for which many specific reversal agents are available, whereas this therapy is often withheld with antiplatelet agents, since use of reversal agents in this context remains controversial.

Patients in Group C had significantly more severe conditions based on the GCS score and pupillary abnormality on admission, higher incidence of hematoma with a mass effect, higher rate of craniotomy, and frequent symptom exacerbation during the clinical course. Thus, in Japan, elderly patients with head injury who are given antithrombotic and reversal agents tend to be those who have intracranial hematoma and require craniotomy or those with an exacerbated status during the clinical course. Subjects with symptom exacerbation in Group C also included those who were transferred to participating facilities due to symptom exacerbation, which explains why the severity on admission was high in Group C. Thus, these results suggest that reversal therapy in Japan is not conducted to prevent symptom exacerbation due to hematoma expansion, but with the aim of performing craniotomy and hematoma evacuation safely to correct the bleeding tendency caused by antithrombotic drugs. Craniotomy was performed in 27 cases in Group C and hemorrhagic complications occurred in 1 case. This gave an incidence of bleeding complications of 3.7 %, which was within the acceptable range.

The poorest outcomes were obtained in patients who underwent reversal therapy (Group C). This may be because brain injury is irreversible and outcomes are not improved in patients with severe conditions, even if craniotomy is conducted safely due to use of reversal therapy. It is important for treatment of brain injury to treat a patient early before disease conditions are exacerbated. The Surgical Trial in Traumatic Intracerebral Hemorrhage (STITCH [Trauma]) study [18] showed improved outcomes in patients with acute subdural hemorrhage who underwent decompressive craniectomy earlier after injury, before the brain was irreversibly damaged. The Clinical Randomization of an Antifibrinolytic in Significant Hemorrhage 3 (CRASH-3) trial [19] confirmed that early administration of tranexamic acid, a hemostatic agent, after injury prevented hematoma expansion and improved outcomes. We investigated the relationship between outcomes and time from injury to administration of reversal agents because reversal therapy has been inferred to have a similar mechanism of action. The results showed a significantly shorter time from injury to administration in patients without symptom exacerbation and in those with favorable outcomes. This indicates the importance of early administration of reversal agents after injury. Further studies are needed to examine the application and timing of reversal therapy for elderly patients with head injury who are given antithrombotic agents, with the goal of promoting use of this therapy.

In this study, 4 subjects (7.6 %) given reversal agents had ischemic complications. Symptom exacerbation during the clinical course

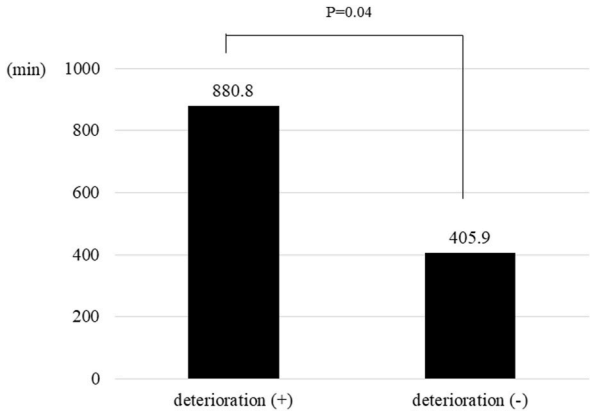

Fig. 1. Time from injury to administration of reversal agents in patients with and without symptom exacerbation. The time in patients without exacerbation was significantly shorter.

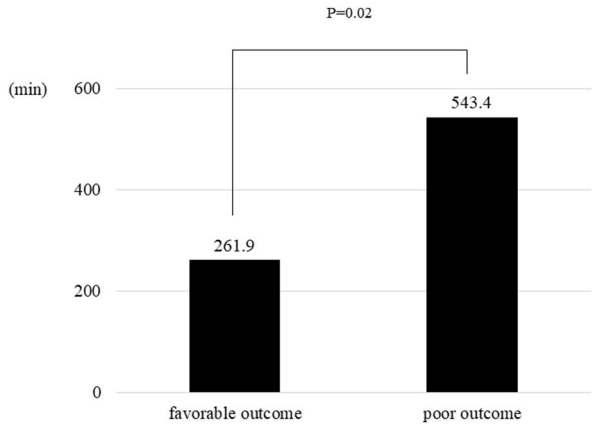

Fig. 2. Time from injury to administration of reversal agents in patients with favorable and unfavorable outcomes. The time in patients with favorable outcomes was significantly shorter.

occurred in 18.5 % of patients given antithrombotic agents, compared to 9.8 % of those not given these agents. There are no concerns with regard to complications of reversal therapy. However, reversal agents are relatively expensive and it will be important to clarify their efficacy in further studies.

This study was an observational evaluation of the current state of reversal therapy for antithrombotic drugs. These drugs include antiplatelet agents and anticoagulants, each of which has different efficacy, and there are also several types of reversal agents for each drug. Thus, the collective evaluation of all of these drugs and agents is a limitation of the study. In the future, it is likely that each reversal agent will be administered under an appropriate protocol to optimize its efficacy.

Also, the study period overlapped with the era of the COVID-19 pandemic. As a result, participating centers experienced a decline in the number of patients with head trauma, due to a general decrease in the number of trauma patients and restrictions on the number of trauma patients who could be treated due to acceptance of COVID-19 infected patients. Such conditions may have had an impact on head injury treatment, and may have influenced the results of this study. This is another limitation of the study.

5. Conclusion

Based on the results of this study, reversal therapy is performed mainly in severe cases requiring craniotomy in Japan, and the threshold is high for mild cases. However, there was some evidence that early reversal therapy can improve outcomes [20,21]. Studies of reversal agents for antithrombotic agents have shown a reversal effect in vivo and a hemostatic effect under certain protocols, but these effects are difficult to confirm clinically due to variation of application and timing of administration. These issues require resolution in further studies.

Ethical consideration

The study was approved by the institutional review board (IRB) at Yamaguchi University School of Medicine (H30-158) and IRBs at participating hospitals. The requirement for patient consent was waived due to the observational design. The study is registered with the University Hospital Medical Information Network (UMIN-CTR, No. 000037283).

Funding information

This work was supported by CSL Behring K.K. United States. Funders were not involved in writing of this manuscript or submission for publication. No authors were paid to write this article by a pharmaceutical company or other agency. The authors had full access to all data in the study and had final responsibility for the decision to submit for publication.

CRediT authorship contribution statement

Eiichi Suehiro: Writing – original draft, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Naoto Shiomi:** Writing – review & editing, Resources, Investigation. **Hiroshi Yatsushige:** Writing – review & editing, Resources, Investigation. **Shin Hirota:** Writing – review & editing, Resources, Investigation. **Shu Hasegawa:** Writing – review & editing, Resources, Investigation. **Hiroshi Karibe:** Writing – review & editing, Resources, Investigation. **Akihiro Miyata:** Writing – review & editing, Resources, Investigation. **Kenya Kawakita:** Writing – review & editing, Resources, Investigation. **Kohei Haji:** Writing – review & editing, Resources, Investigation. **Hideo Aihara:** Writing – review & editing, Resources, Investigation. **Shoji Yokobori:** Writing – review & editing, Resources, Investigation. **Motoki Inaji:** Writing – review & editing, Resources, Investigation. **Takeshi Maeda:** Writing – review & editing, Resources, Investigation. **Takahiro Onuki:** Writing – review & editing, Resources,

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests. Eiichi Suehiro reports financial support was provided by CSL Behring K.K. United States. Eiichi Suehiro reports a relationship with Boehringer Ingelheim, Germany that includes: funding grants. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] Cabinet Office Japan, Annual report on the aging society (2021). https://www8.cao.go.jp/kourei/english/annualreport/2021/pdf/2021.pdf. (Accessed 8 October 2022).

[2] K. Nagata, N. Basugi, T. Fukushima, T. Tango, I. Suzuki, T. Kaminuma, S. Kurashina, A quantitative study of physiological cerebral atrophy with aging. A statistical analysis of the normal range, Neuroradiology 29 (4) (1987) 327–332, https://doi.org/10.1007/BF00348909.

[3] C. Hawley, M. Sakr, S. Scapinello, J. Salvo, P. Wrenn, Traumatic brain injuries in older adults – 6 years of data for one UK trauma centre: retrospective analysis of prospectively collected data, Emerg. Med. J. 34 (8) (2017) 509–516, https://doi.org/10.1136/emermed-2016-206506.

[4] S. Shabani, H.S. Nguyen, N. Doan, J.L. Baisden, Case report and review of Literature of Delayed acute subdural hematoma, World Neurosurg 96 (2016) 66–71, https://doi.org/10.1016/j.wneu.2016.08.075.

[5] F.R. Gerald, M.W. Eric, J.E. Laura, S.A. Lori, B.L. Karyn, The impact of preinjury antiplatelet and anticoagulant pharmacotherapy on outcomes in elderly patients with hemorrhagic brain injury, Surgery 144 (4) (2008) 598–603, https://doi.org/10.1016/j.surg.2008.06.009.

[6] E. Suehiro, Y. Fujiyama, M. Kiyohira, K. Haji, H. Ishihara, S. Nomura, M. Suzuki, The Japan Neurotrauma Data Bank Committee, Risk of deterioration of geriatric traumatic brain injury in patients treated with antithrombotic drugs, World Neurosurgery 127 (2019) E1221–E1227, https://doi.org/10.1016/j.wneu.2019.04.108.

[7] K. Toyoda, M. Yasaka, K. Nagata, T. Nagao, J. Gotoh, T. Sakamoto, S. Uchiyama, K. Minematsu, Bleeding with antithrombotic therapy study group, bleeding with antithrombotic therapy study group: antithrombotic therapy influences location, enlargement, and mortality from intracerebral hemorrhage. The bleeding with antithrombotic therapy (BAT) retrospective study, Cerebrovasc. Dis. 27 (2) (2009) 151–159, https://doi.org/10.1159/000177924.

[8] C.L. Van den Brand, T. Tolido, A.H. Rambach, M.G. Hunink, P. Patka, K. Jellema, Systematic review and meta-analysis: is pre-injury antiplatelet therapy associated with traumatic intracranial hemorrhage? J. Neurotrauma 34 (1) (2017) 1–7, https://doi.org/10.1089/neu.2015.4393.

[9] D. Giakoumettis, G.A. Alexiou, D.A. Vrachatis, K. Themistoklis, P. Stathis, M. Vavuranakis, M.S. Themistocleous, Antithrombotic treatment management in patients with intracerebral hemorrhage: reversal and restart, Curr Pharm Des 23 (9) (2017) 1392–1405, https://doi.org/10.2174/1381612822666161205111459.

[10] J.A. Frontera, J.J. Lewin, A.A. Rabinstein, I.P. Aisiku, A.W. Alexandrov, A.M. Cook, G.J. del Zoppo, M.A. Kumar, E.I.B. Peerschke, M.F. Stiefel, J.S. Teitelbaum, K.E. Wartenberg, C.L. Zerfoss, Guideline for reversal of antithrombotics in intracranial hemorrhage: a statement for Healthcare professionals from the Neurocritical care society and society of critical care medicine, Neurocritical Care 24 (1) (2016) 6–46, https://doi.org/10.1007/s12028-015-0222-x.

[11] S.M. Cho, N. Moazami, S. Katz, R. Starling, J.A. Frontera, Reversal and resumption of antithrombotic therapy in LVAD-associated intracranial hemorrhage, Ann. Thorac. Surg. 108 (1) (2019) 52–58, https://doi.org/10.1016/j.athoracsur.2019.01.016.

[12] M.E. Barra, A.S. Das, B.D. Hayes, E.S. Rosenthal, R.P. Rosovsky, L. Fuh, A.B. Patel, J.N. Goldstein, R.J. Roberts, Evaluation of andexanet alfa and four-factor prothrombin complex concentrate (4F-PCC) for reversal of rivaroxaban- and apixaban-associated intracranial hemorrhages, J. Thromb. Haemostasis 18 (7) (2020) 1637–1647, https://doi.org/10.1111/jth.14838.

[13] B.K. Yorkgitis, D.M. Tatum, S. Taghavi, T.J. Schroeppel, M.R. Noorbakhsh, F.H. Philps, N. Bugaev, K. Mukherjee, M. Bellora, A.W. Ong, A. Ratnasekera, K. D. Nordham, M.M. Carrick, J.M. Haan, K.L. Lightwine, L. Lottenberg, R. Borrego, D.C. Cullinane, J.D. Berne, D.R. Mederos, T.Z. Hayward, A.J. Kerwin, M. Crandall, Eastern Association for the Surgery of Trauma Multicenter Trial: comparison of pre-injury antithrombotic use and reversal strategies among severe traumatic brain injury patients, J. Trauma Acute Care Surg. 92 (1) (2022) 88–92, https://doi.org/10.1097/TA.0000000000003421.

[14] Japan Society of Neurotraumatology (Ed.), Guidelines Committee on the Management of Severe Head Injury, Guidelines for the Management of Head Injury, Igaku-shoin Ltd, Tokyo, 2019, 4th Edition.

[15] G.M. Testerman, S. Shilad, K.J. George, Rapid warfarin reversal with factor VIIa in an elderly trauma patient with retroperitoneal hematoma, Tenn. Med. 102 (3) (2009) 37–39.

[16] D. Dornbos, 3rd, S.M. Nimjee, Reversal of systemic anticoagulants and antiplatelet therapeutics, Neurosurg. Clin. 29 (4) (2018) 537–545, https://doi.org/10.1016/j.nec.2018.06.005.

[17] P. Scotti, C. Séguin, B.W.Y. Lo, E. de Guise, J.M. Troquet, J. Marcoux, Antithrombotic agents and traumatic brain injury in the elderly population: hemorrhage patterns and outcomes, J. Neurosurg. (2019 Jul 5) 1–10, https://doi.org/10.3171/2019.4.JNS19252.

[18] A.D. Mendelow, B.A. Gregson, E.N. Rowan, R. Francis, E. McColl, P. McNamee, I.R. Chambers, A. Unterberg, D. Boyers, P.M. Mitchell, STITCH(Trauma) Investigators, Early surgery versus initial conservative treatment in patients with traumatic intracerebral hemorrhage (STITCH[trauma]): the first randomized trial, J. Neurotrauma 32 (17) (2015) 1312–1323, https://doi.org/10.1089/neu.2014.3644.

[19] CRASH-3 trial collaborators, Effects of tranexamic acid on death, disability, vascular occlusive events and other morbidities in patients with acute traumatic brain injury (CRASH-3): a randomised, placebo-controlled trial, Lancet 394 (10210) (2019) 1713–1723, https://doi.org/10.1016/S0140-6736(19)32233-0.

[20] H.B. Huttner, S.T. Gerner, J.B. Kuramatsu, S.J. Connolly, J. Beyer-Westendorf, A.M. Demchuk, S. Middeldorp, E. Zotova, J. Altevers, F. Andersohn, M. J. Christoph, P. Yue, L. Stross, S. Schwab, Hematoma expansion and clinical outcomes in patients with factor-Xa Inhibitor-related Atraumatic intracerebral hemorrhage treated within the ANNEXA-4 trial versus Real-world usual care, Stroke 53 (2) (2022) 532–543, https://doi.org/10.1161/STROKEAHA.121.034572.

[21] M.B. Pagano, F. Foroutan, R. Goel, E.S. Allen, M.M. Cushing, D.A. Garcia, C.K. Hopkins, K. Klein, J.S. Raval, C.S. Cohn, Vitamin K antagonist reversal strategies: systematic review and network meta-analysis from the AABB, Transfusion 62 (8) (2022) 1652–1661, https://doi.org/10.1111/trf.17010.