Title
Intracranial hemorrhage and platelet transfusion after administration of anti-platelets agents: Fukushima Prefecture

Author(s)
Suzuki, Yuhko; Sato, Taku; Sakuma, Jun; Ichikawa, Masahiro; Kishida, Yugo; Oda, Keiko; Watanabe, Yoichi; Goto, Takeshi; Sato, Masahiro; Nollet, Kenneth E; Saito, Kiyoshi; Ohto, Hitoshi

Citation

Issue Date
2016

URL
http://ir.fmu.ac.jp/dspace/handle/123456789/520

Rights
© 2016 The Fukushima Society of Medical Science

DOI
10.5387/fms.2015-26

Text Version
publisher
Intracranial hemorrhage and platelet transfusion after administration of anti-platelets agents: Fukushima Prefecture

Yuhko Suzuki1), Taku Sato2), Jun Sakuma2), Masahiro Ichikawa2), Yugo Kishida2), Keiko Oda2), Yoichi Watanabe3), Takeshi Goto4), Masahiro Sato5), Kenneth E. Nollet1), Kiyoshi Saito2) and Hitoshi Ohto1)

1)Department of Blood Transfusion and Transplantation Immunology, Fukushima Medical University, Fukushima, Japan, 2)Department of Neurosurgery, Fukushima Medical University, Fukushima, Japan, 3)Department of Neurosurgery, Fukushima Red Cross Hospital, Fukushima, Japan, 4)Department of Neurosurgery, Hoshi General Hospital, Koriyama, Japan, 5)Department of Neurosurgery, Fujita General Hospital, Kuimini, Japan

(Received December 22, 2015, accepted March 24, 2016)

Abstract
We conducted a case series study to assess intracerebral hemorrhage (ICH) in the context of anti-platelets agents (APAs) and platelet (PLT) transfusion in Fukushima Prefecture. This study included patients who were newly diagnosed with ICH between January 2008 and June 2014 in the neurosurgical hospitals of Fukushima Prefecture. Four of ten neurosurgical hospitals responded to our questionnaire. Of 287 ICH patients, 51 (20.6%) were on APA therapy, of whom PLT transfusion was given to only one persistently bleeding patient who was on dual anti-platelet therapy. In a follow-up survey, 30 out of 51 ICH patients on APA therapy, average age 75 years, were analyzed, of whom 21 (70%) were male. The predominant underlying disease was diabetes mellitus. It is interesting to note that peripheral artery disease and aortic aneurysm were among the indications for APAs. ICH was mainly observed supratentorially. Hematoma enlargement was observed in 13 (44.8%) cases. By day 7, 3 patients (10%) had died from complications of ICH. In this study, we show that ICH during APA therapy matched what was observed in Kanagawa Prefecture. Whether or not a national survey differs, we anticipate greater statistical validity and an opportunity to improve patient outcomes in Japan and around the world.

Key words: Anti-platelet agents, Intracranial hemorrhage, Platelet transfusion

Introduction
Japan’s aging society and growing Westernization of lifestyle, including high calorie and animal fat intake, have contributed to the number of people suffering from arteriosclerotic disease1-3).

Among the anti-platelet agents (APAs) widely used around the world, acetylsalicylic acid (aspirin) predominates. The US FDA approved aspirin for secondary prevention of acute coronary syndrome (ACS) in 1985. Japan followed in 2,000, adding aspirin for prevention of arteriosclerotic disease. Many guidelines for coronary heart disease (CHD), cerebral infarction (CI), peripheral artery disease (PAD), diabetes mellitus (DM) and several kinds of arrhythmia recommend ongoing APA therapy for primary and secondary prevention4-9), including dual APA therapy (DAPT) in some guidelines10,11). Along with the advantages of APA therapy, potentially fatal hemorrhagic complications are also recognized12-14). APAs are double-edged swords, especially hazardous in the absence of standardized, reliable protocols to reverse platelet dysfunction.

ICH continues to be a predominant cause of
death in Japan\textsuperscript{15,16}, and worldwide\textsuperscript{17,18}). Focal symptoms depend on the site(s) affected. The usually acute onset means there is no time to stop APAs before ICH. To treat bleeding into the central nervous system, Japanese guidelines recommend higher platelet counts. Many reports and systemic reviews show inferior survival of ICH patients on APA therapy\textsuperscript{19}). Even with many APAs currently in use and no standard reversal protocols, we showed platelet transfusion (PLT) was useful in a single institution’s practice\textsuperscript{20}). Through ongoing dialog with neurosurgeons and emergency physicians, we have recognized various practice patterns and biases in regard to the use of PLT transfusion for ICH patients.

Here we report prefecture-wide practice and outcome data pertaining to: 1) ICH during APA therapy, and 2) PLT transfusion practices in ICH.

Patients and Methods

Ethics: This study (2014, #2062) was approved by the Ethics Committee of Fukushima Medical University, which is guided by local policy, national law, and the World Medical Association Declaration of Helsinki. As this was a retrospective study, informed consent was deemed to be unnecessary, on the condition that patient information was anonymized prior to analysis.

Patients: This study included patients who were newly diagnosed with ICH between January 2008 and June 2014 in the neurosurgical hospitals of Fukushima, a Japanese prefecture of approximately 2 million residents.

Male and female patients at least 20 years old, with recent ICH diagnosed by computed tomography (CT) and no evidence of traumatic cerebral hemorrhage, were eligible for inclusion. Exclusion criteria included intracranial ruptured aneurysm, bleeding arteriovenous malformation, tumor, and if the ICH occurred during pregnancy or just after delivery.

A dedicated multidisciplinary team attended to all surgical and medical issues.

Agents: Aspirin, clopidogrel, and ticlopidine were the predominant APAs in our analyses, as in our previous study\textsuperscript{20}).

Methods: This is a case series study. Initially, we sent a questionnaire to the 10 neurosurgical hospitals in Fukushima prefecture. This questionnaire was to establish how many ICH patients were on APA therapy and whether PLT transfusion was used for any ICH patients with or without APA. As

follow-up, we collected detailed data of ICH patients on APA therapy. The following admission data were collected, reviewed and analyzed as in our previous study\textsuperscript{20}): age; sex; Glasgow Coma Scale (GCS, 3-15; 3 being the worst, and 15 the best); clinical background; complications before onset of ICH; elapsed time, defined as the duration between estimated onset and arrival at our hospital; administration of anti-thrombotic agents (ATAs) including APAs and anticoagulants; and laboratory data on arrival, including prothrombin time (PT), activated partial thromboplastin time (aPTT), platelet count, and fibrinogen. Outcomes on day 7 and day 90 were recorded. Observation time was defined as the duration from the date of onset of ICH to the date of death or to the end of the follow-up, as previously studied.

Results

Four of ten (40\%) neurosurgical hospitals responded to our questionnaire. Fifty-one (20.6\%) out of 287 ICH patients were on APA therapy, among whom PLT transfusion was given to just one patient on dual anti-platelet therapy.

As follow-up, 30 out of 51 ICH patients taking APAs were further analyzed (Table 1 and 2). Their

\begin{table}[h]
\centering
\caption{Characteristics of ICH patients with APAs. (N=51)}
\begin{tabular}{|c|c|c|}
\hline
Factors & Unit & Data \\
\hline
Male & & 21 (70) \\
age & y.o & 75 (67.5, 79.3) \\
Observation time & day & 62 (22, 381.3) \\
Underlying Disease & & \\
Chronic renal failure & & 9 (30) \\
Diabetes Mellitus & & 14 (46.7) \\
Coronary heart disease & & 9 (30) \\
Cerebral Infarction, TIA & & 11 (36.7) \\
Atrial fibrillation & & 4 (13.3) \\
Valvular disease of the heart & & 4 (13.3) \\
Hypertension & & 23 (76.7) \\
Peripheral artery disease & & 1 (3.3) \\
Aortic aneurysm & & 5 (16.7) \\
Coronary risk factors & & \\
0 & & 5 (16.7) \\
1 & & 11 (36.7) \\
2 & & 10 (33.3) \\
3 & & 4 (13.3) \\
\hline
\end{tabular}
\end{table}

Intracranial hemorrhage with anti-platelet agents

The median age was 75 years, of whom 21 (70%) were male and 23 (76.7%) had hypertension. The predominant underlying disease was diabetes mellitus. It is interesting to note that peripheral artery disease and aortic aneurysm were reported in the context of APA therapy. ICH was mainly reported as supratentorial. Hematoma enlargement was observed in 13 (44.8%) cases. By day 7, 3 patients (10%) had died from complications of ICH.

Aspirin was the predominant APA (Table 3). Dual APA therapy was done for 4 (13.3%) patients. Another 8 took warfarin and 1 took rivaroxaban along with their APAs. Other agents with anti-platelets effects, prostaglandin I2 and EPA, were also prescribed for non-arteriosclerotic underlying diseases such as lumbar canal stenosis and hyperlipidemia.

One patient with ICH was given PLTs. Six months prior, he received surgical catheterization and coil embolization for a right intracavernous internal carotid artery aneurysm. Thereafter, he was prescribed aspirin and clopidogrel. He was transferred to our hospital by air ambulance. On arrival, three hours after symptom onset, his CT scan revealed an ICH of 100 cm³ in the left putamen (Figure a). His Glasgow coma score was 7, and his laboratory coagulation profile and other test results were within reference limits. His hematoma rapidly expanded, and his coma progressed. After evacuating the hematoma (Figure b), 10 PLT units were given for oozing (a “unit” is based on what can be derived

| Table 2. Characteristics of ICH patients with APAs. |
|---------------------------------|---------|---------|---------|
| Factors                        | Total number | Unit    | Results     |
| Glasgow coma scale             | 30       | (3-15)  | 14 (7.8, 15) |
| ICH                            | 30       |         |             |
| subcortical                    | 12       | (40)    |             |
| supratentorial                 | 15       | (50)    |             |
| infratentorial                 | 3        | (10)    |             |
| Volume of hematoma             | 30       | cm³     | 26 (4, 84)  |
| Enlargement                    | 30       |         | 13 (44.8)   |
| Laboratory data                |          |         |             |
| platelet                       | 29       | 10^7/μL | 190 (133, 224) |
| prothrombin time               | 29       | %       | 93.2 (46.05, 102.8) |
| aPTT                           | 29       | sec     | 27.6 (24.85, 32.2) |
| fibrinogen                     | 19       | mg/dL   | 278 (223, 318)  |
| Outcome 7th day                | 30       |         |             |
| dead                           | 3        | (10)    |             |
| alive                          | 27       | (90)    |             |


| Table 3. Details of APAs |
|-------------------------|---------|
| Agents                  | Number  |
| ASA                     | 22 (73.3) |
| ASA + Ticlopidine       | 2 (6.7)  |
| ASA + Clopidogrel       | 2 (6.7)  |
| Ticlopidine             | 2 (6.7)  |
| Clopidogrel             | 2 (6.7)  |

APAs : anti-platelets agents. ASA : acetylsalicylic acid (Aspirin)
Numerical variables are given N (%).
from 200 mL whole blood, but in practice PLTs are collected by apheresis. Even then the hematoma expanded (Figure c), but eventually stabilized and regressed (Figure d). No adverse events attributable to PLT transfusion were observed. Thirty days later, he was alive with aphasia and hemiplegia.

Discussion

In this survey of practice and outcomes in Fukushima Prefecture, we found that 20.6% of ICH patients (51 of 267) were on APA therapy before onset, of whom PLTs were transfused to only one patient on DAPT with rapid hematoma expansion after ICH diagnosis. In this cohort, various anti-coagulants were co-administered with APAs before onset. Underlying diseases for which APAs were prescribed were more various than those we reported from Kanagawa Prefecture20).

The rate of ICH with APAs was 20.6% in this survey, versus 15.27% in our previous study20) and 17.9% in the BAT study21). Actually, there is no statistical significance between our two areas; both show around 20% of new ICH patients taking APAs before onset. Among those affected, PLT transfusion and other interventions may be necessary. Among the agents used to reverse APA effects, PLTs act directly to reverse functional interference by APAs. There are opinions in favor of PLTs20,22) and opposed23,24). If effectiveness of PLT transfusion is to be proved, appropriate timing and volume to achieve hemostasis must be addressed. Actually, our patient who received PLT transfusion oozed and his hematoma expanded. He may have needed a larger dose of PLTs, and perhaps subsequent PLT transfusion(s). This patient evoked other questions such as adequate monitoring to confirm the function of platelets, frequency of PLT transfusion, and so on.

The most common barrier to urgent PLT transfusion is availability. Japan’s ageing society reduces the supply of blood donors while increasing the demand for transfusion. Moreover PLT shelf life is only 4 days. In this situation, unassigned PLTs are held at Japanese Red Cross centers. “Just-in-time delivery” is a hallmark of Japanese inventory logistics, but our typical 30-40 minute delay between a clinician’s request and a product’s arrival is unduly long when there is critical bleeding or hemorrhagic stroke risk. The prospect of PLTs derived from induced Pluripotent Stem (iPS) cells is much anticipated25). As for other agents to reverse effects of APAs, recombinant activated factor VII (rVIIa) and DDAVP have been recommended in European and other guidelines26-28), but with little supporting evidence. Moreover, rVIIa is very expensive.

Our survey identified several types of anticoagulants given in conjunction with APA therapy, of which warfarin was the most predominant, with a long history of use and reliable ways to reverse its effects (e.g., vitamin K, fresh frozen plasma) if hemorrhagic complications arise. More recently, several kinds of non-vitamin K antagonist oral anticoagulants (NOACs) have become available, which are more convenient for having fewer hemorrhagic complications29,30), fewer fatal hemorrhagic complications31), and no need for patients to restrict their intake of specific foods such as green vegetables. However, hemorrhagic complication induced by NOACs warrant special concerns different from warfarin, such as giving prothrombin complex concentrate (PCC)32), rVIIa33,34) or specific neutralizing antibodies35).

Finally, underlying diseases in which APAs are given were more various than in our previous study20). Patients with peripheral artery disease (PAD) or aortic aneurysm were observed in this survey. Recently, patients with PAD are increasing in Japan and worldwide, and the use of APAs to reduce mortality following vascular surgery is supported by ACC/AHA guidelines since 201136). So the use of APAs will likely increase.

Now a nationwide survey is underway, assessing management strategies for ICH with APAs, especially, to clarify the advantage of PLT transfusion for ICH with APAs and to optimize the timing and dosing of PLTs. In this pilot study from Fukushima prefecture study, we found the occurrence of ICH with APA therapy was the same as in Kanagawa Prefecture. Whether or not a national survey differs, we anticipate greater statistical validity and an opportunity to improve patient outcomes in Japan and around the world.

Acknowledgements

We thank to cardiologists Prof. Takeishi and Dr. Suzuki for their advice of cardiac guidelines associated with APAs, Mr. Kashimura at the Fukushima Red Cross Blood Center for his up-to-date knowledge of blood supply and demand. Among other colleagues to whom we are grateful, Dr. Aya Goto in FMU’s Department of Public Health and Dr. Yoshiko TAMAI in Hirosaki University Hospital’s department of Transfusion gave excellent advice about our research design.
References


23. Creutzfeldt CJ, Weinstein JR, Longstreth WT, Jr.,


