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Emergency reversal of antiplatelet agents in patients presenting with an intracranial hemorrhage: A clinical review

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Abstract

Objective: Prehospital use of antiplatelet agents has been associated with an increased risk for ICH as well as a secondary increase in ICH volume after the initial hemorrhage. Strategies to reestablish platelet aggregation are used in clinical practice, but without any established guidelines or recommendations. This article serves to evaluate the literature regarding “reversal” of antiplatelet agents in neurosurgical populations.

Methods: PUBMED and MEDLINE databases were searched for publications from 1966 to 2009 relating to intracranial hemorrhage and antiplatelet agents. The reference sections of recent articles, guidelines and reviews were reviewed and pertinent articles identified. Studies were classified by two broad subsets; those describing intracranial hemorrhage relatable to a traumatic mechanism and those with a spontaneous intracranial hemorrhage. Two independent auditors recorded and analyzed study design and the reported outcome measures.

Results: For the spontaneous intracranial hemorrhage group, 9 reports assessing antiplatelet effects on various outcome measures were identified. Eleven studies evaluating the use of prehospital antiplatelets prior to a traumatic intracranial hemorrhage were examined.

Conclusion: The data assessing the relationship between outcome and prehospital antiplatelet agents in the setting of ICH is conflicting in both the trauma and the stroke literature. Only one retrospective review specifically addressed outcomes after attempted reversal with platelet transfusion. Further study is needed to determine whether platelet transfusion ameliorates hematoma enlargement and/or improves outcome in the setting of acute ICH.

Keywords: coagulopathy, antiplatelet agent, intracranial hemorrhage, aspirin, clopidogrel, trauma, stroke, platelet transfusion

Introduction

Prophylactic treatment with anticoagulants and antiplatelet agents has clear benefits in select patients with cardiac and vascular diseases[1, 2]. Over the previous decade, there has been a significant increase in the use of these agents for primary prevention of stroke and heart disease and for prophylaxis and after percutaneous cardiac interventions. Patients experiencing intracranial hemorrhage (ICH) while fully anticoagulated have been reported to present with larger hematoma volumes and suffer a worse prognosis compared to control groups with normal coagulation profiles[3-5]. Further study has demonstrated that ICH progression in anticoagulated patients could be halted, and mortality significantly reduced, with a prompt reversal of anticoagulation[6]. Some investigators have also reported that a prehospital antiplatelet regimen may be associated with hematoma expansion, an increased mortality rate, and a poor functional outcome[7-10]. As such, many institutions have established protocols to “reverse” the impairment of platelet aggregation caused by antiplatelet agents in patients presenting with ICH.

Several antiplatelet agents are commonly used in the outpatient setting. Aspirin is widely used for a variety of indications including risk reduction from transient ischemic

attacks, prevention of primary myocardial infarction, and prevention of colorectal cancer[11]. Aspirin irreversibly binds to the cyclooxygenase-1 (COX-1) enzyme and subsequently inhibits production of thromboxane A₂, a potent eicosanoid involved in platelet aggregation[12]. Non-steroidal anti-inflammatory drugs (NSAIDs) are typically used for relief from arthritis and headache pain. This class of medications acts upon on COX-1 in a reversible, dose-dependent inhibition; as the drug concentration decreases, COX-1 regains its enzymatic activity. Aspirin differs from NSAIDs functionally in that aspirin-induced COX-1 inhibition is irreversible, secondary to protein acetylation[13]. Clopidogrel and ticlopidine both selectively and irreversibly inhibit the P2Y₁₂ ADP receptor. These agents have been used effectively to treat a wide range of cardiovascular and cerebrovascular diseases, such as for prophylaxis after coronary or intracranial stent placement. Due to an active metabolite, clopidogrel in particular persists after cessation of the medication. Some studies have demonstrated a higher incidence of post-operative bleeding with clopidogrel as compared to aspirin, prompting some experts to recommend aggressive anti-platelet reversal for up to 4 days after the last known dose[14].

This review will focus on the treatment of ICH in patients taking prehospital NSAIDS, aspirin and clopidogrel (Plavix), and ticlopidine (Ticlid). Given the heterogeneity of the etiology of intracranial hemorrhages, spontaneous ICH and traumatic hemorrhages will be reviewed separately. The pertinent literature is evaluated and reviewed for evidence-based recommendations or guidelines to provide treatment guidance to clinicians for patients presenting with antiplatelet associated intracranial hemorrhages.

Methods

Literature Review

PUBMED and MEDLINE databases were searched for publications from 1966 to the present using MeSH terms ‘antiplatelet’, ‘aspirin’, ‘clopidogrel (Plavix)’, ‘ticlopidine (Ticlid)’, ‘intracranial hemorrhage’, ‘head injury’, ‘traumatic hemorrhage’, ‘subdural hematoma’, and ‘stroke’. The search was limited to articles in the English language and those relating to human subjects over the age of 18. Reference sections of recent articles, guidelines and reviews were reviewed and pertinent articles identified. Initially, articles identified as relevant were retrieved in abstract format. Full-text manuscripts were subsequently obtained for all original articles applicable to the current review.

Two authors independently evaluated all selected articles (PC, AS). For each study, study design (prospective or retrospective, use of control group, randomization), number of patients included and outcomes of the study were recorded. These results were used to assess if any evidence-based recommendations were able to be made from the literature.

Spontaneous ICH

Spontaneous intracerebral hemorrhage constitutes 10 % to 15% of all strokes and is a devastating stroke subtype. Clinical trials of surgical interventions have failed to demonstrate a consistent benefit[15]. Many predictors of negative outcome have been consistently described in patients suffering from spontaneous ICH, including oral anticoagulant therapy[3, 5]. Furthermore, warfarin use has been associated with larger volumes of ICH on baseline imaging, subsequent ICH growth, and increased mortality[16, 17]. Since hemorrhage expansion is an independent predictor of mortality and poor

functional outcome, established guidelines require the prompt reversal of warfarin-induced effects[18].

Effects on Outcome in Spontaneous ICH

Whether or not antiplatelet medication use at the time of spontaneous ICH influences hemorrhage expansion and neurologic outcome is controversial. Several studies with various designs, sizes, and exclusion criteria have displayed conflicting results (Table 1)[7, 9, 10, 19-23]. While these studies typically report the use of any antiplatelets together in one research arm, aspirin users account for the vast majority of the subpopulation in all studies. The efficacy of platelet transfusion as it relates to outcome was specifically assessed in only one study, but often not in the remainder, thus possibly confounding outcome comparison between the reports[24].

The placebo arms of several randomized studies have been evaluated to determine if any link exists between prehospital antiplatelet use and ICH volume. The Cerebral Hemorrhagic and NXY-059 Treatment trial reported no relationship between prior antiplatelet use and the volume of ICH on baseline CT, ICH growth, or clinical outcome at 90 days[23]. In a phase II trial of rFVIIa for acute ICH, treatment with the recombinant factor and a longer time from onset to baseline CT were related to a decrease in hemorrhage growth in five models of ICH growth; four of the five models found no relationship between antiplatelet use and ICH growth[25]. In these studies, no transfusion of platelets was provided to study participants. Within these studies, at least 80% of the antiplatelet groups were taking ASA alone. The effect of antiplatelet use on outcomes in other prospective and retrospective analyses ranges from non-significant to a

2.7-fold increased 30 day mortality rate and a 7.6-fold increase in hematoma enlargement[7, 9, 10, 19-23].

No study specifically addresses the effects of P2Y₁₂ ADP receptor inhibitors on spontaneous ICH. When a specific agent was specified by the study, clopidogrel and ticlopidine were being taken by 0 to 35.1% of the patients in the antiplatelet arms of studies in the literature[7, 9, 10, 19-23]. Toyoda et al.[10] reported on a series of 251 total patients with 57 antiplatelet users prior to spontaneous ICH. Ticlopidine was used secondary to the lack of availability of clopidogrel in Japan at the time. Twelve patients were on ticlopidine alone and 8 were taking a combination of ticlopidine and another antiplatelet (35.1%). In this series, the use of prehospital antiplatelet agents was an independent predictor for hematoma enlargement (p<0.01), emergent evacuation (p=0.021) and emergent death[10].

Reversal of Antiplatelet Agents in Spontaneous ICH

In the setting of a spontaneous intracranial hemorrhage, attempts to “reverse” antiplatelet-induced effects upon platelets are the mainstay of treatment at most institutions[26]. However, based upon reports pertaining to mostly aspirin users with intracranial hemorrhage, some authors argue these actions are not clinically warranted[27]. While clopidogrel may have a safety profile similar to aspirin, several studies have demonstrated excessive bleeding in various clinical settings[28-31]. Furthermore, a randomized study reported the combination of clopidogrel and aspirin provided significantly more potent inhibition of platelet function when compared to monotherapy with aspirin[32]. To the authors’ knowledge, no report exists dedicated to

outcome comparison in the setting of spontaneous ICH in patients taking pre-hospital aspirin compared with those taking a P2Y₁₂ inhibitor. Given that clopidogrel-induced platelet dysfunction is typically more severe than aspirin; most neuro-intensivists and neurosurgeons continue recommend aggressive reversal of P2Y₁₂ inhibitors in the setting of spontaneous ICH[26].

Traumatic ICH

Traumatic brain injury (TBI) is responsible for more than one million hospital visits, roughly 200,000 hospital admissions, and 50,000 deaths in the United States annually[33]. Given the considerable increase in the use of antiplatelet agents for stroke prevention and cardiac prophylaxis, many patients taking antiplatelet agents will subsequently experience intracranial hemorrhage secondary to TBI. In an attempt to reduce the increased morbidity and mortality associated with TBI in patients on antiplatelet or anticoagulant medications, some centers frequently reverse the effects of antiplatelet agents with platelet transfusion. In a study of anticoagulated patients with traumatic ICH, rapid warfarin reversal led to a reduction in hemorrhage progression and a decrease in mortality ($p < 0.001$)[6]. However, the reversal of platelet dysfunction in patients with TBI on antiplatelet medications has not been fully investigated and no guidelines currently exist regarding this practice.

Effects on Outcome in Traumatic ICH

The current review includes 1 prospective and 10 retrospective studies that have evaluated the outcomes associated with prehospital antiplatelet use in patients admitted

for traumatic head injuries (Table 2)[8, 34-43]. Of the retrospective evaluations, Rozzelle, et al.[35] compared 31 subdural hematoma patients on prehospital antiplatelet agents with controls and found no difference in-hospital mortality, but a 2.6-fold increase in craniotomies for this population. Mina, et al.[36] reported 34 patients with any TBI on preinjury warfarin, heparin, aspirin, NSAIDs, dipyridamole, clopidogrel, or pentoxifylline and found that this diverse group of patients had significantly more deaths when compared with controls not taking any anticoagulation or antiplatelet agents ($p=0.006$). In another retrospective evaluation, Ohm, et al.[38] examined 90 patients with traumatic ICH on prehospital antiplatelets in contrast to 89 matched controls not receiving antiplatelets. In-hospital mortality was 23% in the antiplatelet cohort compared with 8.9% in the control group ($p=0.016$)[38]. Ivascu, et al.[8] evaluated 109 patients on various antiplatelet agents as compared with 42 control patients and discovered those on preinjury antiplatelets were more likely to present with a higher grade hemorrhage than control patients not taking any antiplatelet agents ($p=0.04$). In another large retrospective review, 126 patients with hemorrhagic TBI were compared to controls not on any antiplatelet agent or anticoagulation. No significant differences between the groups were noted, leading the authors to conclude that preinjury antiplatelet or anticoagulant pharmacotherapy did not adversely impact outcome in elderly patients with blunt traumatic ICH[41].

Few studies have isolated the type of antiplatelet agent as it relates to outcome. In a prospective evaluation of the aspirin (ASA) effect upon traumatic brain injury, Spektor, et al.[37] reported 110 patients taking 100mg of ASA with mild or moderate head injury. However, traumatic intracranial hemorrhage was noted in only 27 (24.5%) patients in the

aspirin-treated group and in 31 patients (25.6%) in the control group[37]. Thus, there was no statistically significant increase in the frequency or types of traumatic ICH in low-dose ASA users. Jones, et al.[39] attempted to evaluate the effects of clopidogrel in a general trauma population. Of the 41 patients isolated, only 25 had a head injury and only 9 had a traumatic ICH. While statistical reporting was lacking secondary to the small sample size, a higher percentage of patients in the clopidogrel group underwent cranial surgery, had rebleeding, and required transfusions of blood products than the control group, but mortality and hospital length of stay were not different than controls[39]. In an analysis of patients with traumatic ICH, Wong, et al.[40] reported on 131 patients taking preinjury ASA, clopidogrel and warfarin and found that clopidogrel demonstrated a 14.7-fold increase in the mortality after spontaneous ICH and resulted in a 3-fold increase in disposition to a long-term care facility. Though there are few studies that directly focus upon outcome associated with a specific antiplatelet agent, the two analyzing the use of clopidogrel prior to a traumatic ICH both reported worsened outcomes[39, 40].

Reversal of Antiplatelets in Traumatic ICH

Based on the majority of the studies available, it is conceivable that preinjury antiplatelet therapy may convert a minor traumatic ICH into a progressive ICH[11]. However, currently available studies do not offer recommendations to clinicians on the use of reversal agents for patients with TBI on preinjury antiplatelet therapy. One study assessed patients who received platelet transfusions compared with those who did not to assess outcome differences in the setting of traumatic ICH[43]. In this multi-center

retrospective series, 166 patients with traumatic ICH received platelet transfusions, and 162 did not. The mortality rate for the transfused patients was 17.5%, while mortality for those who did not receive platelet transfusions was 16.7% ($p=0.85$)[43]. Unfortunately, statistical analysis was not reported for any specific anti-platelet agent. Hence, though at first glance it may seem that, as with warfarin, reversal of antiplatelet effects with platelet transfusion should lead to a reduction in mortality and morbidity in the setting of a traumatic ICH, the only study that assessed this hypothesis did not find evidence to support this practice.

Options for Reversal

The literature regarding “reversal” of prehospital aspirin therapy after acute intracranial hemorrhage is equivocal. At many institutions, it is standard practice to recommend platelet transfusion in the setting of intracranial hemorrhage in an effort to stem the salicylate effect upon platelet aggregation[44]. Although there is no specific antidote, the aspirin effect is believed to be reversed by one platelet transfusion (1 single donor or 5 pooled concentrates)[26, 45]. Furthermore, other agents for reversal of the aspirin effect have received basic investigation. Desmopressin seems capable of correcting aspirin-induced platelet dysfunction, although large clinical studies describing relevant outcome parameters have not been undertaken[46-48]. Altman, et al.[49] treated healthy volunteers with aspirin and found that recombinant factor VIIa (rFVIIa) combined with other agonists was able to reverse the anti-aggregating effect of aspirin. No randomized study has been reported outcomes of acute ICH with reference to the reversal the aspirin effect.

Clopidogrel belongs to the class of thienopyridine derivatives, which act by blocking the ADP receptor on the platelet. Like aspirin, no specific antidote exists for the reversal of these agents. In an *ex vivo* study on healthy volunteers given aspirin and clopidogrel, a platelet transfusion consisting of 10 to 12.5 concentrate units successfully restored platelet reactivity[45]. However, given that an active metabolite of clopidogrel persists after cessation of the medication, some experts recommend continued platelet transfusion 4 or 5 days after the last dose of the medication[44]. In another *ex vivo* study of healthy volunteers treated with aspirin plus clopidogrel, rFVIIa reversed the inhibitory platelet effects of these agents[49]. While the clinical utility of desmopressin has not been assessed in the ICH population, Ranucci, et al.[50] reported the antiplatelet effects of clopidogrel and aspirin were partially reversed by an intravenous infusion of desmopressin after carotid endarterectomy. No randomized studies have been reported to assess outcomes after the reversal of thienopyridines in the setting of acute ICH.

Proposed Protocol for Reversal of Antiplatelets

Given the various clinical reports currently available and the absence of any established guidelines in the literature, the current authors' have developed a multi-disciplinary institutional protocol for antiplatelet reversal in the setting of an acute ICH (Figure 1). The authors would like to accentuate the fact that this protocol is based purely upon the recommendations of a local multi-disciplinary team comprised of hematologists, intensivists and neurosurgeons. Patients presenting with an intracranial hemorrhage on ASA alone are given 5 platelet concentrate units upon admission. Those patients presenting with an acute ICH on clopidogrel with small hemorrhages and a neurologic exam that is able to be followed receive an initial transfusion of 10 platelet

concentrate units. For those patients with a severe acute ICH on clopidogrel, 10 units of platelets are transfused initially with 0.3µg/kg of desmopressin, and platelets are subsequently transfused every 12 hours for the next 48 hours. Data regarding clinical outcomes is currently being accumulated.

Discussion

Effect of pharmacokinetics

There is a known substantial variation in patient response to antiplatelet medications[51]. This diversification of molecular effectiveness amongst patients may, in part, explain some of the conflicting outcome results seen in the retrospective reviews presented in Table 1 and Table 2. Recently, Naidech et al.[52-54] reported several studies linking objective measures of platelet function with increased mortality, increased early clot growth, worse functional outcomes at 3 months and intraventricular extension after ICH. These authors used two bedside optical detection systems which measured platelet induced aggregation inhibition due to aspirin and clopidogrel. They determined that abnormal platelet activity results, not the reported use of antiplatelet medications were associated with these negative outcomes and posited that increasing platelet activity may be a more appropriate potential target to improve outcomes after ICH[53]. While more studies at various centers are needed to confirm these findings, these studies provide early evidence that restoring the platelet activity in specifically targeted patients directly upon admission may be of benefit.

Next-generation Antiplatelet Agents

Potent metabolites of the thienopyridines (clopidogrel and ticlopidine) irreversibly inhibit the P2Y₁₂ receptor. Thus, urgent surgical intervention in patients taking these agents is often problematic. From the cardiac literature, clopidogrel treatment within 4–5 days of a coronary artery bypass grafting procedures has been associated with increased blood loss, reoperation for bleeding, increased transfusion requirements, and prolonged intensive care unit and hospital stays[14, 29, 55]. As emergent surgery is often a necessity in the setting of acute coronary syndrome, two direct and reversible P2Y₁₂ antagonists with rapid onset of action have been developed. These new agents, which are currently in Phase III trials, are attractive alternatives to the thienopyridines, especially in situations whereby the rapid inhibition of platelet aggregation or its quick reversal are required[56]. Thus, with the addition of these new P2Y₁₂ inhibitors, physicians will be able to prescribe a more patient-specific antiplatelet regimen based upon individual risk-benefit analysis.

Summary of Findings

The data assessing the relationship between outcomes and prehospital antiplatelet agents in the setting of ICH is contradictory in both the trauma and the stroke literature. The majority of studies reveal a worsened outcome in ICH after taking ASA. After clopidogrel ingestion both dedicated studies in the trauma literature noted worse outcomes, while the study including the highest percentage of patients taking thienopyridines in the spontaneous ICH literature noted worse outcomes as well when compared to controls[10, 39, 40]. Only one retrospective review assessed outcomes after platelet transfusion, the mainstay of antiplatelet reversal at many institutions. Currently,

a randomized trial is recruiting patients in order to determine whether platelet transfusion ameliorates hematoma enlargement in the setting of acute ICH[7]. At present, the literature contains insufficient information to establish any guidelines or treatment recommendations. In light of this, the current authors have proposed a protocol for antiplatelet reversal in both spontaneous and traumatic acute ICH.

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Table 1: Literature review of the effect of antiplatelet agents upon outcome in spontaneous ICH

Table 2: Literature review of the effect of antiplatelet agents upon outcome in the setting of traumatic ICH.

Figure 1: Proposed protocol for reversal of antiplatelet agents in the setting of acute intracranial hemorrhage.

