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Reversing the Effects of Antiplatelet Agents in the Setting of Intracranial Hemorrhage: A Look at the Literature

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Abstract

Patients are increasingly being prescribed antiplatelet agents (APAs) for a growing number of medical and surgical conditions. These agents are associated with an increased risk of hemorrhage, including intracranial hemorrhage (ICH). In the setting of warfarin use and ICH, strategies to reverse the drug effects have improved outcomes. No such strategy exists for APAs, and these patients continue to have poor posthemorrhage outcomes. One strategy is the use of platelet transfusions to provide functional, circulating platelets. Studies have shown mixed results regarding the benefit of this practice. Other strategies include the use of desmopressin and recombinant factor VIIa. More studies are necessary to delineate the effectiveness of the various strategies.

Keywords

antiplatelet agents, intracranial hemorrhage, platelet transfusion, clopidogrel, aspirin

Introduction

Hemorrhagic stroke is a disabling condition with a high mortality rate, which affects thousands of individuals in the United States every year.[1] An increasing number of patients are being prescribed with antiplatelet agents (APAs) for clinical conditions such as coronary artery disease, stroke, transient ischemic attack, and peripheral arterial disease in order to decrease the risk of arterial thrombosis. Patients taking APAs are susceptible to bleeding complications, including intracranial hemorrhage (ICH). In addition, many patients take over-the-counter medications such as aspirin (ASA) or herbal supplements that inhibit platelet function. Among all of the patients admitted with ICH, 10% to 30% have been taking ASA or clopidogrel.[1-3] The addition of ASA to a clopidogrel regimen increases bleeding risk, including the risk of life-threatening bleeding[4]; however, the combination of the 2 drugs is more effective in preventing ischemic events.[5]

The ASA is rapidly absorbed enterally and reaches peak plasma levels 30 to 40 minutes following ingestion. It works by inhibiting the cyclooxygenase (COX) enzymes COX-1 and COX-2, preventing the conversion of arachidonic acid to thromboxane-A_2, which is a potent activator of platelets. This inhibition of the platelets is permanent; therefore, despite the short half-life of ASA in circulation (15-20 minutes), ASA has a lasting effect on platelet function. The ASA has shown benefit in many studies in patients at risk of arterial thrombosis, and although the risk of ICH associated with ASA use is low (<1% per year), the effects can be devastating[6] (Figure 1).

The action of clopidogrel requires conversion into its active metabolite by the liver following administration. The active metabolite is short lived in the plasma. Clopidogrel works by irreversibly inhibiting the platelet P2Y 12 receptor, therefore, preventing platelet activation by adenosine diphosphate (ADP). Other thienopyridines (ticlopidine and prasugrel) work by similar mechanisms of action, although their pharmacokinetics vary slightly.[6]

The platelet impairment caused by ASA and/or clopidogrel likely decreases the efficacy of primary hemostasis. When bleeding occurs, platelets are activated by exposed collagen at the site of the damaged endothelial cells. Activated platelets undergo shape change and degranulate releasing prothrombotic substances at the site of vascular injury. This helps to initiate and perpetuate secondary hemostasis through the clotting cascade, further contributing to clot formation. Because of the impairment of thromboxane formation (ASA) and ADP receptor function (clopidogrel), primary hemostasis is at the very least blunted in the setting of these 2 medications, which likely leads to further bleeding.

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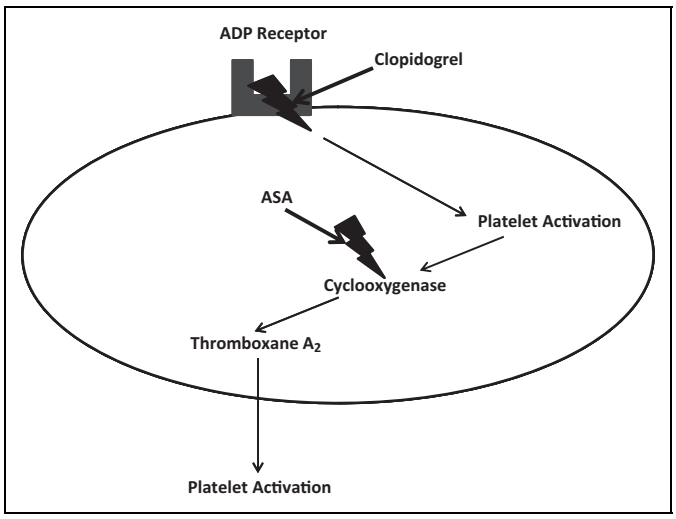

Figure 1. Clopidogrel inhibits platelet function by irreversibly blocking (nonsterically) the adenosine diphosphate (ADP) receptor on the surface of the platelet. Aspirin (ASA) irreversibly inhibits the cyclooxygenase enzyme, therefore, preventing thromboxane production. Thromboxane is a potent activator of platelets.

The Problem

Spontaneous ICH is a devastating result of many causes and comprises 10% to 15% of all strokes.[7] Individuals at risk of cardiac disease and stroke, who are on preventative APAs, often have risk factors for ICH including hypertension and atherosclerotic vascular disease. Preventive APAs are the most common cause of acquired platelet dysfunction.[8] As previously stated, individual institutional studies have shown that 10% to 31.3%[1-3] of the patients admitted to the hospital with ICH were taking APAs prior to admission. Hematoma expansion occurs early in up to one-third of the patients with spontaneous ICH[7]and can be associated with poor outcome.[1,9-11] Multiple studies have been done to evaluate the influence of APAs in patients with ICH, and there have been mixed results.[1-2,12-17]

A Japanese study reviewing 251 patients with ICH found that the initial hematoma volume in those patients taking APAs was actually less than that of patients not taking APAs. However, patients taking APAs had statistically significant increased risk of acute hematoma expansion and surgical evacuation of the hematoma.[13] This study did not look at clopidogrel because of its lack of availability in Japan. Another group found that patients taking APAs had a 40% inhospital mortality rate when compared to those patients on oral anticoagulants (28%) and patients not taking antithrombotic medications (23%).[11] A study by Creutzfeldt et al of 368 patients with spontaneous ICH found that the use of APAs prior to admission was associated with an increased risk of mortality (odds ratio 2.4).[2]

Caso et al looked prospectively at patients with a first ICH who had been taking APAs for at least 7 days. They found that the use of antiplatelet medications was not associated with increased mortality or disability.[3] Another prospective study, however, found significantly increased mortality in patients taking ASA prior to ICH when compared to non-ASA users; however, the mortality was less than those taking oral anticoagulants such as warfarin.[12] Another group found that, among other variables, the previous use of APAs was an independent predictor of 30-day mortality. This was particularly true for ASA.[15] A meta-analysis looking at APAs in ICH showed that APA use had an association with increased mortality but not functional outcome after adjusting for factors in a multivariate analysis. The increased mortality is possibly related to hematoma expansion in patients with APA use. Variations in reporting functional outcomes may contribute to the nonsignificance of this factor in the meta-analysis.[18] Thus, there is a considerable variability in the results of the studies looking at the impact of APAs on outcomes in patients who present with ICH.

A study looking at in vitro platelet function (with or without the use of antiplatelet medications) as demonstrated by VerifyNow (Accumetrics, San Diego, California) showed that impaired platelet function was associated with increased hematoma volume.[14]

Evaluating Platelet Function in the Setting of APAs

Platelet function testing, for evaluating the ongoing effects of ASA and clopidogrel, is not widely available. This is, in part, due to the lack of proven results of the point-of-care instruments currently available and to the complexity of other methods. Currently available testing includes platelet aggregation (light transmittance and impedance), platelet function analyzer 100 (PFA-100; Siemens Healthcare Diagnostics, Terrytown, New York), VerifyNow (Accumetrics), and Thrombelastography (TEG) Platelet Mapping (Haemonetics, Braintree, Massachusetts). Each of these tests has its limitations. Platelet aggregation is not readily available in urgent settings. The PFA-100 instrument measures clotting by passing whole blood through a capillary tube with a small aperture coated with an agonist that stimulates platelet aggregation. This test is sensitive to ASA therapy, but it is nonspecific and does not detect clopidogrel effects. There are cartridges to assess both ASA and clopidogrel effect for the VerifyNow instrument using a small amount of whole blood, but correlation with other laboratory tests of platelet function is poor. In TEG Platelet Mapping, the platelet contribution to clotting is measured with a thrombin-generated clot, and these results are compared to the platelet component of a clot induced by either ADP or arachidonic acid. The difference between the tests (the thrombin-generated clot vs the agonist-generated clot) indicates the presence or absence of a drug effect on platelet function. The TEG Platelet Mapping has little correlation with standard laboratory testing, however, and can be cumbersome to perform. With the currently available testing platforms, platelet function testing is controversial in this setting, and the best method (if any) is yet to be determined. Furthermore, the clinical utility of such tests for decision making in the setting of an acute ICH has not been clarified.

Table 1. A Summary of the Published Literature on the Use of Platelet Transfusion in the Setting of ICH in Patients Taking APAs.

Author	Total No. Patients	No. Patients Taking			Total No. Transfused, %	Platelet Dose	Conclusion
		APAs	ASA (No. Transfused)	Clopidogrel (No. Transfused)			
Retrospective							
Downey et al[17]	328	328	NA	97 (74)	166 (51)	NA	Platelet did not improve transfusion in ICH
Creutzfeldt et al[2]	368	121	118	16	53 (44)	NA	Found no significant benefit due to platelet transfusion
Ducruet et al[1]	762	65	51 (25)	14 (9)	35 (54)	5.6 ± 5 (clopidogrel) 4.3 ± 4.3 (ASA)	No benefit due to platelet transfusion on mortality, length of stay, or outcome
Washington et al[23]	321	108	92 (38)	36 (23)	44 (41)	1.1 ± 0.9	No improvement due to platelet transfusion on outcomes
Prospective							
Naidech et al[16]	68	68	68	6	16 (24)	NA	No association between platelet transfusion and ICH volume
Naidech et al[19]	45	32	22	10	45 (100)	1-2 apheresis units	Platelet transfusion leads to in vitro improvement in platelet function

Abbreviations: APAs, anti-platelet agents; ASA, aspirin; NA, not available; ICH, intracranial hemorrhage.

The Use of Platelet Transfusion in ICH

Although there is some debate about whether or not APAs influence outcomes in patients with ICH, there is even less guidance about how to reverse the effect of APAs, and whether or not such reversal affects outcome (Table 1). The first question to answer is whether or not transfusing platelets improves platelet function. An in vitro study was performed to answer this particular question. Light-transmittance aggregometry and flow cytometry were used to determine the influence of platelet transfusion on platelet function in normal healthy volunteers taking ASA and clopidogrel. Platelet function studies were performed at baseline and at the scheduled sample draw times. Platelet-rich plasma pooled from individuals not taking APAs was added to the samples in various concentrations, and platelet function was retested. They concluded that the equivalent of 2 to 3 platelet pools (1 platelet pool = 5 whole blood-derived platelets) would normalize platelet function in patients treated with APAs.[20]

In a retrospective study looking at clinically significant hematoma formation as determined by computed tomography scan, no significant difference was found in hematoma volume (initial or final) in patients transfused with platelets compared to those not transfused. More patients who were taking clopidogrel were transfused than those who were not taking the drug. Interestingly, only 28% of the transfused patients received a platelet transfusion within 2 hours of presentation to the hospital.[1] The conclusion of this study was that platelet transfusion was not beneficial in patients presenting with ICH who were taking APAs. These findings were similar to those by Downey et al who did not find a significant difference in mortality rates in patients receiving platelet transfusions compared to those who were not transfused.[17] Other retrospective studies also show that platelet transfusion does not appear to influence outcomes in patients taking APAs prior to spontaneous ICH.[2]

Most often, platelets are given because of anecdotal experience with the notion that the dysfunction can be overcome if the patient has an adequate number of circulating functional platelets derived from transfusion.[21] This is supported by in vitro studies of platelet function.[19] In guidelines published jointly by the American Heart Association and the American Stroke Association, the use of platelet transfusions in patients with ICH on antiplatelet medications is considered investigational.[22] More studies are necessary to validate the effectiveness of this practice as well as to determine the proper dose of platelet transfusion.

A study design was recently published to address the question of whether or not platelet transfusions are useful. The platelet transfusion in cerebral hemorrhage (PATCH) study will prospectively look at 190 patients with ICH who are on APAs from 38 hospitals in the Netherlands. The patients will be randomized to receive platelet transfusion within 6 hours of the onset of symptoms or to receive standard care. The outcome at 3 months will be evaluated as the primary end point. The platelet transfusions will consist of a single transfusion of a pool of 5 or 10 buffy coat-derived platelets.[11] We are unaware of any literature to suggest that platelet transfusions contribute to ICH expansion.

The Effect of ASA and Clopidogrel on Transfused Platelets

The question of whether or not ASA or clopidogrel will affect transfused platelets is more difficult to answer. ASA has a half-life of approximately 2 to 4.5 hours,[1] while clopidogrel has a

half-life of approximately 8 hours.[21] Both the drugs irreversibly inhibit platelet function. Both the drugs are metabolized in the liver. The function of clopidogrel is dependent on the liver metabolism via the cytochrome P450 enzyme 2C9 to the active metabolite (a thiol derivative), whereas the metabolite of ASA is inactive.[21] In vitro studies have shown that platelet transfusion can lead to an increase in the platelet functional activity in the setting of APAs.[16,20] Furthermore, based on the lack of an active metabolite and a peak effectiveness of 1 to 2 hours after ingestion, it is unlikely that ASA will affect platelets transfused after that time period. Although there is a lack of definitive evidence regarding an adverse functional effect on transfused platelets, 1 retrospective study has shown an increase in hematoma expansion in patients taking clopidogrel despite platelet transfusions.[1]

Risks of Platelet Transfusions

There are many risks associated with empiric treatment of patients taking APAs with platelet transfusions, which can potentially lead to higher morbidity and mortality rates in transfused patients. In the retrospective study by Washington et al, both deaths were due to cardiac issues following (but not necessarily precipitated by) platelet transfusion.[23] Naidech et al found an adverse event rate of 16% in those patients transfused with platelets.[19] Transfusion risks include transfusion-related acute lung injury, transfusion-associated cardiac overload (TACO), septic transfusion reactions, and allergic transfusion reactions, among others. Of particular note, many of the patients who present with ICH and are taking APAs have a history of cardiac disease, which may predispose them to complications of transfusions, especially TACO.

Alternatives to Platelet Transfusion to Improve Platelet Function

A number of alternative treatments have been tried in patients with platelet dysfunction secondary to APAs. Desmopressin (DDAVP) has been used to correct the effect of ASA[24] and can be given at a dose of 0.3 mcg/kg by slow intravenous infusion.[25] This has been shown to increase platelet function as evidenced by the bleeding time following ASA.[25] There are minimal complications of DDAVP therapy, including headache and rhinitis. Recombinant-activated factor VII (rFVIIa) has also been used, but the risk of thrombosis needs to be considered relative to the benefits of controlling the bleed.[8,21] A retrospective study failed to demonstrate the benefit associated with the infusion of rFVIIa in patients with ICH.[26] Another approach that has been tried is the use of antifibrinolytic agents such as aprotinin. In vitro investigations of platelet function using Plateletworks (Helena Lab, Beaumont, Texas) showed correction of platelet function following aprotinin infusion in patients with greater than 10% inhibition due to clopidogrel.[27] Aprotinin, however, is no longer available in the United States. More research is needed in this area because treatment options are very limited at present.

Restarting APAs Following ICH

There is little guidance in the literature regarding reinitiating APA therapy following ICH. A meta-analysis looking at APA therapy in aneurysmal ICH showed a trend toward improved outcomes in patients treated with APAs, which is hypothesized to be due to reduced secondary ischemia following the hemorrhage.[28] In recently published American Heart Association guideline, the recommendation was made that APA therapy could be considered after the resolution of the acute phase of the ICH.[22] Clinical comorbidities and risk factors need to be considered prior to restarting APA therapy.

Conclusions

The use of platelet transfusions to correct acquired platelet dysfunction due to the use of APAs in patients who present with ICH has not yet been conclusively demonstrated to affect outcomes, but there is some evidence that platelet function is improved. More prospective studies are necessary to more clearly delineate whether a difference in outcomes exists in patients who receive platelet transfusion compared to those who have not. As in all the cases of transfusion of blood products, the risks of the transfusion need to be weighed against the risk of other treatments.

Timing may be the key to the effectiveness of platelet transfusions in the setting of ICH. Most hematoma growth occurs within 6 hours of the onset of the symptoms of ICH[11]; however, many of the patients described in the studies were not transfused until much later in the course of their hemorrhage. One or 2 units of single-donor apheresis platelets (or the equivalent) at presentation should provide adequate numbers of functional platelets for hemostasis. If given early enough in the course of ICH, platelet transfusion may be potentially effective in counteracting the effects of APAs and, with the short plasma-life of ASA, transfused platelets are unlikely to be affected by this medication. The likelihood of effect is less clear in the setting of clopidogrel. If platelet transfusion is not effective or the volume of a transfusion cannot be tolerated, alternative products such as rFVIIa should be considered after weighing the risks of thrombosis associated with these products.

As more and more patients are being prescribed with APAs, this question of how to reverse the effects of APAs will only expand. There is a growing need for prospective trials such as the PATCH trial.[11] Focusing on early intervention with prompt transfusion after diagnosis may be the key to the success of platelet transfusion in these patients. Platelet function testing, if available, may help to guide platelet transfusion therapy in the setting of APAs.

In patients with ICH who have been taking APAs, despite the lack of definitive evidence, it would seem reasonable, until such definitive evidence becomes available, to transfuse 1 to 2 units of single-donor apheresis platelets to provide functional platelets, especially if these platelet transfusion can be administered within 6 hours of the onset of symptoms.

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