Approach to the Anticoagulated Patient with Spontaneous ICH

By James R. Roberts, MD

Individuals with spontaneous intracranial hemorrhage (ICH) are common denizens of every ED. The public is relatively clueless about the nefarious and debilitating effects of brain hemorrhage, and often think patients who have had a hemorrhagic stroke can get back to normal through the prowess of highly skilled physicians, especially if everything is done correctly. While this might be somewhat true for a modicum of fortunate survivors, bleeding brains usually continue to bleed, and dead brain usually stays dead. Fortunately, rehabilitation of other areas of the brain and the body’s remarkable reparative processes offer some respite from certain paralysis or a long-term vegetative existence. But exactly what doctors can do to help the acutely bleeding brain or enhance potential recovery is still quite a mystery.

Last month’s column began a series of discussions on the ED approach to ICH, focusing on what to do with the ICH victim’s blood pressure. I concluded that the nuances of manipulating blood pressure during the initial throes of a hemorrhagic CVA continue to confound and perplex. The peccadilloes and vagaries of blood pressure control bewildered even the most erudite clinician, and have eluded researchers worldwide. Attempting to decipher the thorny pathophysiology of the ravenous ICH victim’s blood pressure could be an opportunity to help patients who may be an opportunity to help patients who have had a hemorrhagic stroke.

The combination of IV vitamin K and fresh frozen plasma (FFP) is recommended to reverse warfarin-induced coagulopathy in ICH. Neither alone is sufficient. It takes at least 12 to 24 hours or more to accomplish complete reversal, however, so one wonders if this intervention actually benefits the patient or simply makes the INR look better. No rigorous studies have answered this question, and the outcome of ICH is still dismal despite the near-immediate cessation of active bleeding with rFVIIa or prothrombin complex concentrates. These expensive antidotes will reverse the errant INR in less than an hour, but have not been proven to rescue the patient from the ravages of intracranial hemorrhage. rFVIIa is not recommended by current guidelines. My hospital does not carry any expensive antidotes will reverse the errant INR in less than an hour, but have not been proven to rescue the patient from the ravages of intracranial hemorrhage. rFVIIa is not recommended by current guidelines. My hospital does not carry any PCCs, which is why they are not included in the photograph.

This publication is an update of the prior 2007 AHA-ASA Guidelines. The section of interest is the evaluation and treatment of patients with severe coagulation factor deficiency, or severe thrombocytopenia, who suffer a spontaneous ICH. The AHA and ASA consider those to be patients on oral anticoagulants, those with acquired or congenital coagulation factor deficiency, and those who have quantitative or qualitative drug-induced platelet abnormalities. In the ED, patients will be either anticoagulated with warfarin or taking aspirin and/or clopidogrel (Plavix). About 15 percent of patients with ICH are anticoagulated, and the number of patients taking antiplatelet drugs is increasing. Both subgroups are at risk for spontaneous ICH. The authors are sanguine that there may be an opportunity to help patients who bleed with a coagulopathy-platelet abnormality, with hopes of decreasing morbidity and mortality.

In general, anticoagulated patients with life-threatening hemorrhage, including ICH, should have their INR normalized as rapidly as possible. The traditional recommendation has been the combination of IV vitamin K and fresh frozen plasma (FFP). Although not generally available, a variety of prothrombin complex concentrates (PCC) and recombinant factor VIIa (rFVIIa) also have been suggested as potential therapies to reverse coagulopathies.

While an ideal antidote for warfarin-associated hemorrhage, vitamin K requires a number of hours to correct the INR, hours that continue to wreak havoc on the bleeding brain. IV administration has rarely been associated with anaphylactoid reactions. FFP has a minimal downside of allergic and infectious complications, but the basic processing time is, at best, one to two hours, and multiple clinical logistics can delay administration. A significant volume of FFP is required for complete INR reversal. Even when given under current guidelines, as many as 17 percent of patients

Continued on next page
The downside of PCCs, other than minutes in the patient taking warfarin.

administration can normalize the INR within coagulation factors that are deficient have a high concentration of specific II, VII, IX, and X. They have been increasingly recommended for warfarin reversal. PCCs act rapidly because they have a high concentration of specific coagulation factors that are deficient in warfarin-treated patients, and one infusion can normalize the INR within minutes in the patient taking warfarin. The downside of PCCs, other than their lack of readily availability and cost, is that they may increase the risk of thromboembolic complications. There have been no large, controlled, randomized prospective trials evaluating the use of PCCs to rapidly reverse warfarin, and the use has been largely anecdotal and via retrospective analysis. This article has a table of commercially available PCCs, but not all are available in the United States. None has been rigorously studied or compared head-to-head with vitamin K and FFP.

rFVIIa is officially licensed to treat hemophilia in patients with high titer inhibitors or coagulation factor VII deficiency. It has been studied as a potential treatment for spontaneous bleeding from a number of causes unrelated to hemophilia, for example, as a general coagulant for multiple trauma and ICH in the absence of prior anticoagulation. The American Society of Hematology, however, promulgated an evidence-based recommendation against the routine use of rFVIIa for warfarin reversal, partly because it does not replenish all the vitamin K dependent factors. (Hematology Am Soc Hematol Educ Program 2008;26-30; Blood 2010;116[5]:675.) Despite its favorable effect on laboratory measurements, rFVIIa may not be an effective antidote for warfarin. Other interventions are considered superior because there is no high-quality evidence supporting the efficacy of rFVIIa for warfarin reversal. rFVIIa has been studied in a few randomized trials for treating ICH, and the results have been equivocal, with no clear understanding of risks or benefits. If given within four hours of ICH, rFVIIa limits hematoma growth in some studies, and may provide some improved clinical outcome relative to placebo. There is an increased frequency of thromboembolic events, at least a threefold difference. (New Engl J Med 2005;352[8]:777.) Even though the INR is corrected and the clot ameliorated, other studies have failed to show a significant difference in clinical outcomes. But every time this drug was studied, there was an increased incidence of new thromboembolic events. (New Engl J Med 2005;358[20]:2127.) The AHA and ASA conclude that it remains to be determined whether rFVIIa will benefit a particular subset of patients with ICH. Currently any benefit remains unproven, and the use of rFVIIa is not recommended as a warfarin antidote for spontaneous ICH by the AHA and ASA in these most recent guidelines.

The increasing use of antplatelet agents, which essentially produce platelet dysfunction, has been a subject of much interest in ICH. Currently, the effect of antplatelet agents with regard to rFVIIa use in patients with ICH is unsettled, with extant trials yielding conflicting results. It is not certain that the use of antplatelet agents will worsen hematoma expansion or worsen clinical outcome. (Stroke 2009;40[7]:2385.) This is counterintuitive, and the issue remains confusing. Simply stated, there is no proof that reversing drug-induced platelet dysfunction is helpful or required for ICH. The utility and safety of platelet transfusions in patients with a normal platelet count and who are taking these medications is also unknown. Such an intervention has not been posited as standard intervention.

A summary of new recommendations for the treatment of coagulation factor deficiency or severe thrombocytopenia appears in table 1. As a new class I, level of evidence C recommendation, patients with a severe (undefined) coagulation factor deficiency or severe thrombocytopenia (undefined) should receive appropriate factor replacement therapy instead of platelets, respectively. Patients who are taking warfarin who have an INR elevated more than 1.5, per these recommendations, should receive therapy to replace vitamin K dependent factors and correct the INR to normal. The treatment to correct the coagulopathy always includes IV vitamin K, but other agents are combined to augment and facilitate full and more rapid reversal. These other current options include a PCC or FFP.

The AHA and ASA waffle on the use of FFP versus PCC. Some studies have used them together. Without regard to FFP use, total coagulopathy reversal may not occur because it does not replace all clotting factors, even though the INR number may be lowered. For this reason and because of other complications, rFVIIa is not routinely recommended as a sole agent for warfarin reversal in ICH. The increased risk of
thromboembolic events, primarily arterial as opposed to venous, has limited the use of rFVIIa, and have negated a formal recommendation, at least until further studies are performed.

The AHA and ASA did not recommend platelet transfusion in the presence of ICH in patients who are taking antiplatelet therapy because the benefit is unclear and still under investigation. There is no recommendation for a specific intervention for patients taking clopidogrel or aspirin.

Comment: These recommendations are not hugely different from the prior ones, and are still somewhat vague, hedging, and certainly limited by rigorous data. IV vitamin K, despite some concern about anaphylactoid reactions, is recommended for all warfarin-anticoagulated patients. The use of “something else” to augment vitamin K is suggested, however. From my reading, this “something else” should be FFP. The dose of FFP is 10-15 ml/kg to raise the factor levels by 15 percent to 20 percent and to be effective against warfarin-induced coagulopathies. Additional use is guided by the INR. It is stressed that FFP takes time to work, actually quite a bit of time when one is dealing with a brain bleed. Getting FFP in the ED is always labor intensive; nonetheless, it’s about all we have. FFP certainly works more quickly than vitamin K alone but comes with an increased but likely tolerable complication rate. In a very slim 70 kg patient on warfarin, an oddity for most with ICH, at least 1050 ml of FFP is needed to reverse the INR. Importantly, this may not be achieved with any great regularity for at least 24 hours. Note that in obese patients, the volume requirement is more, and the fluid load may be problematic. One unit of FFP has about 250 ml volume, so your initial order should be for ABO crossmatching for four to six units. Once thawed, give it all. Unusual thawed FFP is viable for five days, and it cannot be re-frozen so it is discarded if not used.

Berplex/PN (a human prothrombin complex concentrate containing factors II, VII, IX, X and inhibitors of Protein C and proteins S) sounds promising. This product can normalize INR elevations from warfarin in about 30 minutes. (ClinicalTrials.gov: http://bit.ly/berplex; Crit Care 2008;12[4];R105; Am J Hematol 2008;83[2]:137.)

Table 1: American Heart Association and American Stroke Association Recommendations

1. Patients with a severe coagulation factor deficiency or severe thrombocytopenia should receive appropriate factor replacement therapy or platelets, respectively. (Class I; Level of Evidence: C) (New recommendation) Note: severe is not defined.

2. Patients with ICH whose INR is elevated due to oral anticoagulants (OACs) should have their warfarin withheld, receive therapy to replace vitamin K-dependent factors and correct the INR, and receive intravenous vitamin K. (Class I; Level of Evidence: C)

PPCs have not shown improved outcome compared with FFP but may have fewer complications compared with FFP, and are reasonable to consider as an alternative to FFP. (Class IIa; Level of Evidence: B).

rFVIIa does not replace all clotting factors, and although the INR may be lowered, clotting may not be restored in vivo; therefore, rFVIIa is not routinely recommended as a sole agent for OAC reversal in ICH. (Class III; Level of Evidence: C) (Revised from the previous guideline.) Note: Vitamin K plus FFP or PCC is recommended.

3. Although rFVIIa can limit the extent of hematoma expansion in non-anticoagulated ICH patients, there is an increase in thromboembolic risk with rFVIIa and no clear clinical benefit in unselected patients. Thus rFVIIa is not recommended in unselected patients. (Class III; Level of Evidence: A) (New recommendation) Further research to determine whether any selected group of patients may benefit from this therapy is needed before any recommendation for its use can be made.

4. The usefulness of platelet transfusions in ICH patients with a history of antiplatelet use is unclear and considered investigational. (Class IIb; Level of Evidence: B) (New recommendation)

Because the reversal of warfarin-induced coagulopathy takes time and patients with ICH don’t have much time, the EP is in a bind for empiric over- or underordering, over- or under-treating, or waiting for a tardy laboratory and noncompliant consultants. It is axiomatic that patients with ICH who are taking warfarin should have a stat INR. It’s not mandated by a guideline to administer empiric vitamin K or FFP to all comers just because they are taking warfarin, and even ordering FFP prior to INR results can waste this valuable blood product. Even though IV vitamin K is a common recommendation by all, the last thing such patients need is an anaphylactoid reaction. I have not personally seen anaphylactoid problems from IV vitamin K, although it has a bold black box warning and there are scary case reports. (J Thromb Thrombolysis 2001;11[2]:175.)

The AHA and ASA recommend 10 mg IV. There are no stern cautions on how to give the vitamin K. I give it over 10 to 15 minutes, and start with a 10 mg dose in the seriously ill patients. Some authors suggest a 20 mg dose for ICH. Of course, reversing warfarin coagulopathy in patients without ICH has become a very modest and somewhat limited intervention. An INR of 5 does not now prompt reversal in the asymptomatic nonbleeding patient.

It makes intuitive sense to administer platelets to patients who have

Continued on next page
ICH

Continued from previous page

thrombocytopenia in the presence of ICH. The AHA and ASA offer no guidelines whatsoever on the exact level of thrombocytopenia that should prompt platelet transfusions, except using the term “severe.” In general, platelet levels have to drop below 50,000 mm³ to be of concern for other indications, but I have not seen any guidelines for platelet transfusions in ICH. Using “below normal” as a guideline likely would result in significant overtreatment for patients with modest inconsequential thrombocytopenia.

Many patients take platelet inhibitors for their coronary stents and other cardiovascular indications. These patients with their comorbidities are prime candidates for ICH. Clopidogrel not produce thrombocytopenia per se, but does decrease function of native platelets, which theoretically can increase bleeding in spontaneous ICH. At the current time, exactly what to do with these patients is unsettled, and the current recommendations do not proffer any specific intervention. In the future, one may be able to reverse the platelet dysfunction easily, but currently the patient is stuck with less-than-ideal platelets while they are bleeding in the head. There are no unequivocal data demonstrating a higher morbidity and mortality in patients taking these agents, but it makes sense that such a relationship might exist.

Safety of Recombinant Activated Factor VII in Randomized Clinical Trials

Levi M, Levy JH, et al


These authors analyze data from 35 randomized clinical trials to investigate the frequency of thromboembolic events in patients receiving recombinant activated factor VII (rFVIIa) for so-called “off-label” indications. Many medications are used off-label, so this tactic by itself is not unusual. The only formal recommendation for rFVIIa is for treating bleeding in patients with hemophilia A or B who have inhibiting antibodies to coagulation factor VII or IX. Patients with hemophilia also receive it prior to surgery or when they have a bleeding episode. rFVIIa has been used to treat life-threatening hemorrhage, even in the patient with normal coagulation parameters, but there is a potential increased risk of thromboembolic complications because of the drug’s clotting facilitation.

Clopidogrel’s mechanism of action could staunch severe life-threatening bleeding in patients with many clinical conditions. Such conditions, all of them technically off-label, were thought to be fair game to study for rFVIIa use, including severe traumatic injuries, controlling bleeding during surgery, treating ICH, and managing bleeding due to anticoagulation therapy. Because such patients are at high risk for death from their massive bleeding, it only made sense to attempt to reverse coagulopathy or help the body clot in general.

rFVIIa is administered in doses about 1,000 times the physiologic level with a half-life of about 2.5 hours. Prior studies have shown thromboembolic (hypercoagulable) events, particularly arterial, in one to two percent of patients receiving rFVIIa during off-label use. Patients being administered rFVIIa were obviously quite ill, had significant comorbidities, and interpretation of any data would be difficult. These authors pooled data to further analyze the potential for thromboembolic events, and some of the studies included patients with ICH.

Data were obtained from almost 45,000 patients enrolled in 35 placebo-controlled trials. The bottom line was that there was an increased statistical risk of arterial thromboembolic events in patients given off-label rFVIIa vs. placebo. Coronary thrombosis was 2.6 times higher than placebo, and the risk was highest in elderly patients. Patients with ICH are generally elderly and at greater risk. Another common arterial thrombotic event was cerebral infarction. Although there is also a potential for venous thromboembolic events (DVT/PE) with this drug, this analysis did not find that the rate of the venous events was statistically elevated. Non-letal venous thrombosis (“phlebitis”) was found in a small number of normal human volunteers who participated in the early manufacturer-sponsored trials. Despite the findings, the authors of this study do not take a firm position on prohibiting rFVIIa in patients with ICH, but take the stance that a risk-benefit consideration should be employed.

An accompanying editorial notes that the off-label use of rFVIIa is relatively common (at least 4%), but the exact incidence is unknown. (New Engl J Med 2010;363(19):1853.) The off-label use of rFVIIa, per this author, “warrants scrutiny,” with the caveat that thrombotic sequelae are “not consequential.” Neither the article nor the editorial offers a definitive prohibition of the use of rFVIIa in coagulopathic patients with ICH. The risk of both coronary and cerebral thrombotic events with the use of this drug complicates its once-promising future for patients with CNS bleeding.

Comment: rFVIIa does not have zeal- ous support for ICH, regardless of the INR, but our current knowledge is incomplete. There does not appear to be convincing evidence for the use of rFVIIa for treating spontaneous ICH in the ED, even if patients are anticoagulated with warfarin and have a high INR. Without doubt, the INR will be normalized with rFVIIa, and the patient will look better on paper. Although it seemed like a good idea and perhaps some patients will have their clot size minimized and rapidity of growth decreased, it is unclear whether this once heralded interven- tion will result in better patient outcome. If we have not proven it yet, I suspect that we likely will not in the future unless a specific subgroup can be identified as prime candidates for rFVIIa.

It is very disconcerting to watch a patient continue to bleed in his brain. EPs have a lot to consider: Should we empirically transfuse vitamin K and FFP before the INR is back? Can we limit or halt bleeding, and if so, will it help in the long run? Can we chance rFVIIa? Does the body know best, and can we allow the natural history of ICH to sort out the best course? Should one attempt to aggressively stop the bleeding with experimental therapies?

An epiphany did not lead me to conclude that ICH is a bad disease. If we are intellectually honest and can get over physician hubris, we must conclude that so far we have little to offer most patients with ICH other than doing no harm and tweaking the vital signs with the hope that bodies will respond to allow a modicum of survival and maximal neurologic function. It seems reasonable to reserve coagulopaties and fix thrombocytopenia, but currently even these therapies are not miracles. If it takes 24 hours to normalize the INR, how can that possibly be a life vs. death intervention?

Bottom line for ICH: Obtain an INR and platelet count, administer vitamin K and FFP if the INR is greater than 1.5, and pick a platelet level at which you feel correction would be helpful. (Maybe 50-100,000/mm³?) Then you and the family might best turn to prayer. While these interventions are clearly emergency medicine turf, it’s always best to seek consultation, and get the patient to the neurointensivist’s turf rapidly. Then get ready to share with your consultant colleagues the minimal praise you might garner if you actually restore someone to even near-normal CNS function. Also, gear up for the more common overwhelming criticism and all-too-common liability components that might follow no matter what you do with ICH, basically a near-death sentence for most victims of this hellacious affront to the brain.

EMN
February 2011

EMN
emn@lww.com

Click and Connect! Access the links in this article by reading it on www.EM-News.com.

Dr. Roberts is the chairman of emergency medicine and the director of the division of toxicology at Mercy Catholic Medical Center, and a professor of emergency medicine and toxicology at the Drexel University College of Medicine, both in Philadelphia.

Table 3.

OFF-LABEL USE OF RFVIIA: RISK FOR THROMBOEMBOLIC EVENTS

<table>
<thead>
<tr>
<th>Overall arterial thromboembolic events²</th>
<th>In patients given rFVIIa</th>
<th>In those given placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increase in complication rate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In those 65 and older given rFVIIa</td>
<td>5.5%</td>
<td>3.2% (p=0.003)</td>
</tr>
<tr>
<td>In those 65 and older given placebo</td>
<td>3.8%</td>
<td>10.8%</td>
</tr>
<tr>
<td>In those 75 and older given rFVIIa</td>
<td>10.8%</td>
<td></td>
</tr>
<tr>
<td>In those 75 and older given placebo</td>
<td>4.1%</td>
<td></td>
</tr>
</tbody>
</table>

1. There is no significant increase in venous thromboembolic events.
2. Primarily coronary artery occlusion and cerebral infarction.