Treating Warfarin-Related Intracerebral Hemorrhage
Is Fresh Frozen Plasma Enough?

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Intracranial hemorrhage, specifically spontaneous intracerebral hemorrhage (ICH), is the most feared complication of warfarin therapy. Although occurring infrequently (<1% per year) in clinical trials of warfarin and stroke prevention in nonvalvular atrial fibrillation, the real risk in community practice may be higher. Warfarin worsens the severity of hemorrhage and dramatically increases the risk of mortality from ICH. Because of this, most consensus guidelines for the management of anticoagulation-related intracranial hemorrhage recommend urgent correction of the international normalized ratio (INR) to near normal values while acknowledging the lack of randomized trials addressing this treatment approach.

In this issue of Stroke, Goldstein et al describe their experience at a single institution regarding the effectiveness of an anticoagulation reversal strategy which used primarily fresh frozen plasma (FFP) and, in most cases, vitamin K. Of 69 patients included in the analysis, 57 (83%) had successful reversal of warfarin coagulopathy (defined as an INR ≤ 1.4) within 24 hours of arrival in the emergency department (ED). The group of patients with successful INR reversal within 24 hours had a significantly shorter duration from ICH diagnosis (defined as time of computed tomography scan) to initiation of FFP infusion. Patients who received FFP earlier tended to be older, more neurologically impaired (lower Glasgow Coma Scale score), and have a higher INR, although none of these differences were statistically significant. Patients transferred from an outside hospital had an almost doubling of the mean time to FFP initiation (208 minutes versus 113 minutes; P = 0.003). Each additional 30-minute delay in FFP administration decreased the odds of successful INR reversal by 20%. Despite these findings, earlier time to treatment with FFP and INR reversal at 24 hours did not translate to improved clinical outcome.

This study has significant limitations (most acknowledged by the authors). The retrospective nature of the study, the need to exclude 46 subjects from the cohort because of missing ED records, and the lack of uniform times of INR testing limit the ability to make some firm conclusions, especially regarding the impact of timing of INR reversal on outcome. Confounding by indication (in which sicker patients received FFP earlier) remains a possibility despite attempts to adjust for patient characteristics. Even so, the authors rightly point out that the times to FFP initiation seem remarkably long for an emergency intervention. This is actually not surprising given the inherent delay introduced by the need to thaw stored FFP before administration. The authors raise concern that the lack of outcome benefit may be because FFP administration in this cohort was too late to stop ongoing bleeding, which is the presumptive mechanism whereby anticoagulation reversal would be of benefit. Some patients did not receive vitamin K in the ED, and no patient received prothrombin complex concentrate (PCC) or recombinant factor VIIa. Thus, this manuscript likely reflects a “real world” experience, especially in the United States, which is unsatisfactory in an era of acute stroke intervention.

The sole reason to reverse the effect of anticoagulation in a patient with warfarin-related ICH is to stop hematoma enlargement attributable to ongoing hemorrhage. Hematoma enlargement very early after nonwarfarin ICH is a current topic of great interest, and initial results using recombinant factor VIIa are encouraging. Patients with warfarin-related ICH are even more likely to undergo hematoma expansion, and the time course of this expansion may occur over a longer period than nonwarfarin ICH. Although no prospective randomized trials exist comparing different methods of warfarin reversal, there is growing recognition, bolstered by the Goldstein article, that FFP alone is insufficient. Small case series using PCC and recombinant factor VIIa strongly suggest that these compounds normalize the INR much more quickly than FFP, often within an hour or two. In fact, current consensus guidelines from the US, UK, and Australia recommend that for patients with “life-threatening” warfarin-related bleeding, PCC (when available), intravenous vitamin K, and FFP should all be administered. PCCs (which are usually a powder containing factors IX, II, X and low levels of factor VII) have the potential advantage that they can be mixed and administered more quickly than FFP. However, at least in the United States, PCCs have somewhat limited availability and are not extensively used.

One of the most concerning findings of the Goldstein study is that 1 in 6 patients did not even have INR reversal a full day after diagnosis despite the fact that these patients presumably represented a group that were intended for aggressive management. The authors should be lauded for their willingness to share the shortcomings of their prior experience; they also emphasize that their findings have led to dissemination of formal guidelines within their own institution. Heterogeneity in the use of various anticoagulant reversal strategies is a
concern not only in the US.\textsuperscript{11} The lack of randomized trials examining the benefit of successful and early INR reversal leaves open the possibility that anticoagulation reversal is not beneficial and that a normalized INR is only a surrogate outcome without clinical correlate. However, current consensus guidelines are fairly uniform and it seems prudent to consider any ICH in a patient with an elevated INR from warfarin as “life-threatening.”

We are now firmly in the era of acute stroke intervention. Acute stroke teams administer tissue plasminogen activator and other treatments within the first few hours after acute ischemic stroke. Recombinant factor VIIa administration within the first 4 hours of non–anticoagulation-related ICH is being studied. Warfarin-related ICH needs to be considered within the context of acute stroke intervention. Time is brain. Immediate correction of coagulopathy is the goal, and hospitals should have acute protocols for this treatment just as they do for early treatment of other types of stroke.

Randomized trials for warfarin-related hemorrhage are probably justified. The real question is whether trials are needed solely in order to justify existing consensus guidelines (which emphasize the use of PCC when possible, in addition to vitamin K and FFP) or whether we are ready to move beyond these guidelines and address other issues such as differences in factor replacement strategies (eg, PCC, factor VIIa) or time windows from symptom onset. The available evidence suggests that FFP alone (with vitamin K) is probably not enough. However, we must walk before we can run. In order to truly change practice on a wide scale it behooves us to turn consensus into evidence and prove that we have something better.

\textbf{References}


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