

EVMS- EM Journal Club
 9/20/10
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P: In patients taking warfarin who present with spontaneous ICH
 I: Is reversal of the coagulopathy with Prothrombin Complex or rFVIIa
 C: compared to INR correction to less than 1.4 with FFP
 O: Associated with improved clinical outcomes?

A 70yo female is brought to ED by EMS with AMS. She was found poorly responsive in a chair by her husband 30 minutes ago. Pt takes warfarin for Atrial fibrillation. INR in the ED is 5. She weighs 80 kg. CT of the head reveals moderate sized intracranial hemorrhage.

Quick Facts:

Half of patients with oral anticoagulant-associated ICH die within 30 days. ¹
 Approximately one third of ICH will increase in size by 30% within 24 hrs. ²

Article	Patient Group	Study Type	Outcome	Key Results	Weakness
<i>Prothrombin complex concentrate for emergency anticoagulation reversal: a prospective multinational clinical trial.</i> Pabinger, I. et al. J of Thromb and Haemostasis 2008; 6: 622-31.	43 Patients with INR >2 requiring urgent reversal for either emergent procedure/surgery, or acute bleeding. (26 requiring procedure, 17 with acute bleeds)	Prospective multicenter (15) study 25, 35, 50 IU/kg PCC doses based on INR 88% of pts also received Vit K.	Normalization of INR to <1.4 by 30 min Hemostatic efficacy based on physician rating of cessation of bleeding or blood loss during procedure.	93% INR normalization by 30 min 98% Hemostatic efficacy No evidence of viral transmission 58% adverse events 2 suspected thromboembolic complications.	Small sample size No control group, no randomization Physician bias in rating "hemostatic efficacy" Ties to industry

<p><i>Comparison of FFP and PCC for reversal of OAC in patients undergoing cardiopulmonary bypass: a randomized study.</i> Demeyere, R. et al. Intl J of Transfusion Medicine 2010;99: 251-260</p>	<p>40 pts INR >2 undergoing semi-urgent CPB surgery received EITHER: 2 units FFP Or Half dose PCC calculated by body weight and INR (Repeated after initiation of CPB to target INR 1.5) Mean age: 70.4 Mean INR: 2.7</p>	<p>-Prospective, randomized controlled trial -Single center</p>	<p>Number of pts reaching target INR (<1.5) at 15 min Number pts reaching target INR at 1 hour PostOp bleeding, blood transfusions, HCT, serum levels of Vit K dependent factors.</p>	<p>At 15 min, target INR reached by: 7/20 in PCC group 0/20 in FFP group (p=0.007) No difference at 1 hr More pts in FFP group needed additional doses Similar AE rate (43.8% vs 56.3%)</p>	<p>-Small sample size -Does not address ICH directly -Not blinded -Unknown significance of administering 2 half-doses in stead on single dose.</p>
<p><i>Emergency reversal of anticoagulation after intracerebral hemorrhage.</i> Fredriksson, K. et al. Stroke 1992; 23(7):972-7</p>	<p>17 Pts with OAC associated ICH. Treated with either PCC (n=10) or FFP (n=7) in addition to Vit K</p>	<p>Retrospective chart review.</p>	<p>-Mean drop in INR over time -S/S of ICH based on Reaction level scale</p>	<p>PCC mean INR decreased from 2.83 to 1.22 over 4.8 hrs, symptom progression 0.2 RLS FFP mean INR decreased from 2.97 to 1.74 over 7.3 hrs (p<0.001), RLS progression 1.9 (p<0.05)</p>	<p>-Small sample size -Dose determined by treating MD -Subjective nature of RLS -Trend toward improved outcomes is not significant</p>
<p><i>Recombinant activated factor VII for acute intracerebral hemorrhage.</i> Mayer S, et al.</p>	<p>399 pts with ICH by CT treated with either placebo or rFVIIa (40, 80, 160mcg/kg)</p>	<p>Prospective, Randomized Controlled Trial</p>	<p>Percent change in volume of ICH at 24 hrs. Clinical outcomes at 90 days. (death or severe disability)</p>	<p>29% volume incr placebo 16% 40mcg 14% 80mcg 11% 160mcg (p=0.01)</p>	<p>-Possible conflict of interest -“use with caution in pts at risk for thromboembolic events”</p>

NEJM 2005; 352:8.			Thromboembolic events	64% mortality placebo 55% 40mcg 49% 80mcg 54% 160 mcg (p=0.004) 0% arterial TE events placebo 5% rFVIIa (p=0.01)	-Need to determine appropriate dose for ICH -Unblinded
<i>Efficacy and safety of rFVIIa for acute intracerebral hemorrhage.</i> Mayer, S, et al. NEJM 2008; 358:20	841 pts with ICH by CT treated with either placebo or rFVIIa (20, 80 mcg/kg) within 4 hrs of onset	Prospective Randomized Controlled Trial	Poor outcome: death or severe disability by modified Rankin scale at 90 days	No significant difference in poor outcomes. No survival benefit. Increased risk of arterial TE events in 80mcg group: 9% vs 4% in placebo (p=0.04)	-Possible conflict of interest -Subjective nature of clinical assessments -Unblinded -Included pts with h/o TE disease, previously excluded -“Randomization imbalances” More baseline IVH in treatment group
<i>Thrombotic Events with Recombinant Activated Factor VII in Spontaneous ICH. (FAST Trial).</i> Diringer, MN et al. Stroke 2010;41:48-53 45:205-207	841 Pts with CT confirmed ICH within 3 hrs of symptom onset, given either 20 or 80 mcg/kg rFVIIa or placebo.	Prospective Randomized controlled trial.	Incidence of arterial and venous thromboembolism Identifying risk factors for TE	No difference VTE Arterial events: 27% placebo 26% low dose 46% high dose (p=0.04) MI: 13% placebo 9% low dose	-Possible conflicts of interest -Subjective determination of TEs “possibly related to rFVIIa”

				19% high dose TE Risk factors: Age Antiplatelet agents Baseline signs of ischemia High dose rFVIIa	
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Clinical Bottom Line:

In patients with oral anticoagulant-associated ICH, there is Level I evidence to support holding warfarin, replacing vitamin K-dependent factors and giving IV vitamin K.

There is also reasonable (Level IIa) evidence to consider using PCC as an alternative to FFP, as it corrects INR faster and appears to have fewer complications.

More research is needed to identify the patient populations that would most benefit from receiving treatment with recombinant Factor VIIa. At this time rFVIIa is NOT recommended for reversal of INR in patients with OAC-associated ICH. (Level III evidence).

References

1. Aguilar MI, Hart RG, Kase CS, Freeman WD, Hoeben BJ, Garcia RC, Ansell JE, Mayer SA, Norrving B, Rosand J, Steiner T, Wijdicks EF, Yamaguchi T, Yasaka M. Treatment of warfarin-associated intracerebral hemorrhage: literature review and expert opinion. Mayo Clin Proc 2007; 82: 82–92.