Critical Review Form

Therapy

Use of Recombinant Factor VII in Patients With Warfarin-Associated Intracranial Hemorrhage, *Neurocritical Care* 2005; 2:1-6

Objective: **Intracranial hemorrhage in patients on warfarin requires rapid correction of clotting function. Current therapy involves administration of Vitamin K and Fresh Frozen Plasma. The authors sought to gather preliminary data on the addition of Factor VII to usual therapy, its effectiveness in correcting the INR and its safety.**

Methods: **A retrospective Barnes-Jewish Hospital chart review by a single investigator (DL Brody) without clearly stated methods of warfarin associated hemorrhage identified by reviewing discharge summaries of all patients with intracranial hemorrhage admitted over an 11-month period (March 2002 through January 2003). Patients were included if they were taking warfarin, had an ICH, and had an INR>1.3. All patients were admitted to the Neurological ICU, and treated with vitamin K (10mg IV/SQ, then 10mg SQ daily for an additional 2 days) and FFP. In addition to the above, selected patients received Factor VII based upon one or more of the following: a hematoma expansion related clinical deterioration; increased risk of developing FFP related complications; or a need for urgent neurosurgical intervention. Candidacy for treatment with Factor VII was determined by the treating physicians. Patients who received Factor VII were identified through the blood bank, where use of Factor VII must be approved. Patients who received Factor VII were compared to those who did not. Outcomes included time from diagnosis to correction of INR below 1.3 AND time from initial order to administer Factor VII until normalization of the INR. Thrombotic complications attributable to Factor VII included MI, cerebral infarction, and DVT. Complications related to FFP were sought, such as pulmonary edema, transfusion reactions and infection.**

Guide		Comments
I.	**Are the results valid?**	
A.	**Did experimental and control groups begin the study with a similar prognosis (answer the questions posed below)?**	No, this was a retrospective chart review comparing two cohorts, not a randomized trial.
1.	Were patients randomized?	No, this is a retrospective study.
2.	Was randomization concealed (blinded)?	Not randomized.
3.	Were patients analyzed in the groups to which they were randomized?	Not randomized.

4.	Were patients in the treatment and control groups similar with respect to known prognostic factors?	Authors state that the differences are "not significant", however, the *FVIIa group* had higher APACHE II scores, longer ICU stays, lower GCS at discharge. (Table 1). Several of the Factor VII patients were given this medication specifically because they were deteriorating with usual care, due to hematoma expansion. Factor VII was given to those who were felt to be more at risk for CHF, and those who needed urgent surgery. INR at presentation was comparable for both groups. In summary, the FVIIa group probably represented a sicker population to begin with thus skewing the analysis against FVIIa in terms of overall mortality.
B.	**Did experimental and control groups retain a similar prognosis after the study started (answer the questions posed below)?**	
1.	Were patients aware of group allocation?	Patients were not blinded to their treatment, so some may have been aware of medications they were given.
2.	Were clinicians aware of group allocation?	Yes.
3.	Were outcome assessors aware of group allocation?	Yes.
4.	Was follow-up complete?	No loss to follow-up was reported.
II.	**What are the results (answer the questions posed below)?**	

1.	How large was the treatment effect?	**Efficacy in Correction of INR** (Table 2) Time from presentation to INR less than 1.3 median: 8.8 hours for FVIIa group (range 1.8-130h), and 32.2 hours (range 10-72.8h) for the FFP group. Thus, an approximate four-fold decrease in the time to correction of INR (p=0.016). Time from the decision to give FFP to correction of INR was also calculated at 5.1 hours. **Volume of FFP Required**--mean +/- SD (range) FVIIa group—1272+/-782(0—2475) ml FFP group—2044+/-773 (780—3484) ml (p=0.022) **Adverse Effects—FVIIa** (out of 13 pts. treated Two patients developed thrombotic complications—one of these two died. **Adverse Effects—FFP** (out of 15 pts. treated) One patient developed CHF that responded to furosemide. Therefore, **Factor VIIa appears to correct the INR in one-fourth the time with one-half the FFP required when Factor VIIa is not utilized.**
2.	How precise was the estimate of the treatment effect?	Precision is likely poor, although the authors provide insufficient data to even calculate confidence intervals which they do not report. They do provide ranges. There was no standardized time table for serial INR measurement. Perhaps INR was checked more frequently in those who were deteriorating due to hematoma expansion, or in those who required urgent surgery. The authors attempt to deal with this by analyzing the intervals between the first and second INR measurement for the two groups, which was felt to be not statistically significant. What about the intervals between the 2nd and 3rd (or later) measurements? Precision for measurement of the volume of FFP administered to the two groups is also unclear, but probably good, since the volume of FFP given to a patient is documented well in most charts Confidence Intervals not Provided.

III.	**How can I apply the results to patient care (answer the questions posed below)?**	
1.	Were the study patients similar to my patient?	Yes. They were, in fact, patients from our population.

2.	Were all clinically important outcomes considered?	The time to correction of INR is a surrogate outcome measure, intuitively thought to estimate or be correlated with outcomes of importance: mortality and discharge functional status. Neither of these was considered.
3.	Are the likely treatment benefits worth the potential harm and costs?	This study is not adequate to answer the question. However, it does highlight a possible beneficial treatment effect that could be elucidated in a RCT. Complications such as arterial and venous thrombosis were alluded to in the study, but no statistical analysis of their frequency was performed. In addition, there was no evaluation of the financial cost of this expensive therapy.

<u>Limitations</u>:

1) **A retrospective study without clearly stated methods: was the data abstractor trained, blinded, and monitored? Were standardized data abstraction forms utilized? However, the stated aim of this study was not to be definitive in establishing one treatment as superior to the other, but rather to generate some preliminary safety and laboratory efficacy data for comparing the two treatment options.**

2) **FVIIa group was demonstrably sicker. In fact, it was specifically used on patients who were sicker, and clinically deteriorating.**

3) **There were no predetermined criteria for administration of FVIIa—a decision left to treating physicians—leading to *selection bias*. Additionally, the lack of blinding of clinicians (*ascertainment bias*) or outcome assessors (*verification bias*) may have also impacted the findings and introduced systematic error.**

4) **Treatment and control groups both received FFP. Therefore, it is not possible to make any statements regarding efficacy of FFP vs. FVIIa alone.**

5) **There was no standardized time when the INR was supposed to be checked on these patients.**

6) **It is unclear how well correction of INR, a test that is sensitive to Factor VII levels, correlates with correction of coagulopathy in vivo. There is as yet no consensus as to the most appropriate assay with which to monitor treatment with factor VII. Factor VII Clotting Activity (FVIIC), for example, is used to monitor its use in hemophiliacs with inhibitiors.**

<u>Bottom Line</u>:

In the setting of warfarin-associated ICH, FVIIa plus FFP and Vitamin K appears to correct INR four-fold faster than FFP and Vitamin K alone with one-half the volume of FFP. A sufficiently powered randomized controlled trial of FVIIa in the setting of warfarin associated ICH will be necessary to definitely assess the efficacy and safety of this novel, expensive therapeutic alternative.