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Journal club critique

Recombinant factor VIIa in severe trauma: further study needed

Dan A. Galvan[1] and Mitchell P. Fink[2]

[1] Clinical Fellow, Department of Critical Care Medicine, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA
[2] Professor and Chair, Departments of Critical Care Medicine, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA

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Expanded Abstract

Citation

Boffard KD, Riou B, Warren B, Choong PI, Rizoli S, Rossaint R, Axelsen M, Kluger Y: Recombinant factor VIIa as adjunctive therapy for bleeding control in severely injured trauma patients: two parallel randomized, placebo-controlled, double-blind clinical trials. J Trauma 2005, 59:8-15 [1].

Background

Uncontrolled bleeding is a leading cause of death in trauma. Two randomized, placebo-controlled, double-blind trials (one in blunt trauma and one in penetrating trauma) were conducted simultaneously to evaluate the efficacy and safety of recombinant factor VIIa (rFVIIa) as adjunctive therapy for control of bleeding in patients with severe blunt or penetrating trauma.

Methods

Design: Two parallel randomized, placebo-controlled, double-blind clinical trials.

Setting: Thirty-two hospitals throughout Australia, Canada, France, Germany, Israel, Singapore, South Africa, and the United Kingdom.

Intervention: Severely bleeding trauma patients were randomized to rFVIIa (200, 100, and 100 μg/kg) or placebo in addition to standard treatment. The first dose followed transfusion of the eighth red blood cell (RBC) unit, with additional doses 1 and 3 hours later.

Outcomes: The primary endpoint for bleeding control in patients alive at 48 hours was units of RBCs transfused within 48 hours of the first dose.

Results

Among 301 patients randomized, 143 blunt trauma patients and 134 penetrating trauma patients were eligible for analysis. In blunt trauma, RBC transfusion was significantly reduced with rFVIIa relative to placebo (estimated reduction of 2.6 RBC units, $p = 0.02$), and the need for massive transfusion (>20 units of RBCs) was reduced (14% vs. 33% of patients; $p = 0.03$). In penetrating trauma, similar analyses showed trends toward rFVIIa reducing RBC transfusion (estimated reduction of 1.0 RBC units, $p = 0.10$) and massive transfusion (7% vs. 19%; $p = 0.08$). Trends toward a reduction in mortality and critical complications were observed. Adverse events including thromboembolic events were evenly distributed between treatment groups.

Conclusion

Recombinant FVIIa resulted in a significant reduction in RBC transfusions in severe blunt trauma. Similar trends were observed in penetrating trauma. The safety of rFVIIa was established in these trauma populations within the investigated dose range.

Commentary

Uncontrolled bleeding is a major cause of death in trauma. Considerable controversy exists regarding the role of recombinant activated factor VIIa (rFVIIa) for the control of severe hemorrhage in trauma, although case series and anecdotal reports have shown promise [2-5]. Dr. Boffard and colleagues [1] confronted this issue by carrying out two relatively large prospective, randomized clinical trials of rFVIIa in severely bleeding trauma victims. One trial enrolled patients with severe blunt trauma (n=143) and the other enrolled patients with penetrating trauma (n=134). The authors reported a statistically significant reduction in red blood cell (RBC) transfusion and the need for massive (>20 unit) transfusion in blunt trauma patients treated with rFVIIa. There was a trend favoring rFVIIa in the penetrating trauma group. There were no differences in adverse events, such

as thromboembolism or mortality, between the treatment groups in either of the studies. The observed treatment effect was independent of clinical center.

This complex, international, multi-center study was a carefully planned experimental trial with clinically relevant findings. There are, however, several limitations that deserve consideration. To be eligible for this trial, patients had to have evidence of severe bleeding (transfusion of at least 6 units of RBCs within 4 hours of admission). Fortunately, few trauma patients meet this requirement [6]. Therefore, the results of this trial are applicable to a relatively small subset of trauma patients. The drug seemed to work best after blunt trauma rather than penetrating trauma. The authors suggest this observation may reflect that blunt trauma is more often associated with diffuse ("nonsurgical") bleeding, whereas penetrating trauma is more often associated with major arterial or venous injuries that require surgical, as opposed to pharmacologic, control.

In order to be included in the primary analysis, patients had to be alive 48 hours after the first dose of study drug. This requirement was necessitated by the study's primary endpoint; patients who die early have less time to be transfused, so a drug that helps patients to live longer could paradoxically increase the likelihood for transfusion. In other words, for the comparison to be fair, subjects had to have equal time at risk. While this is entirely appropriate, it does make interpreting the number needed to treat (NNT) to avoid massive transfusion a bit challenging. Since the reported NNT actually represents the number of non-dead patients that would need to be treated, this number is only useful if one could know in advance who will live or die within 48 hours. Therefore, it would have been helpful for the authors to have also reported the NNT for all patients. In secondary analyses, the authors did explore the effect of including all patients. While the between-group differences were no longer significant, the direction of the effect remained the same.

The authors used a one-sided statistical test to analyze the RBC transfusion data because "it was not expected that administration of rFVIIa would increase transfusion requirements." In general, one-sided p-values are often viewed with skepticism by statisticians and clinicians. If the authors' aim was to change practice, they might have presented a more convincing argument by using a two-sided approach instead. The study was not powered to detect a mortality difference, although 30-day mortality was non-significantly lower for rFVIIa treated patients (blunt trauma: 25% vs. 30%, p=0.58; penetrating trauma: 24% vs. 28%, p=0.69). With a larger trial, these differences might have become significant, which would have made the approximate $20,000 cost of the drug regimen easier for clinicians (and pharmacy and therapeutic committees) to justify. To enable more judicious and, perhaps, more cost-effective use of this drug, it would be useful to establish criteria to predict when rFVIIa might be futile, such as in the setting of profound acidosis and coagulopathy [7].

Recommendation

The finding that rFVIIa may reduce RBC transfusions is important but only lends credence to the argument that further trials are needed. Questions regarding minimal effective dose, number and frequency of doses, and the indicated patient population (and conversely, the population which would not benefit from this drug) creates a field ripe for further exploration. Given its expense, formal cost-effectiveness analyses should be an integral component of all future trials.

Competing interests

DAG declares no competing interests. MPF reports that he has served as a consultant for NovoNordisk, the manufacturer of rVFIIa.

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