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Critique of 'Recombinant Activated Factor VII Safety in Trauma Patients: Results from the CONTROL Trial'☆

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☆Critique of: Richard P. Dutton, Michael Parr, Bartholomew J. Tortella et al. Recombinant Activated Factor VII Safety in Trauma Patients: Results from the CONTROL Trial, *The Journal of TRAUMA Injury, Infection, and Critical Care*. Volume 71, Number 1, July 2011

ABSTRACT

Background: Safety data on recombinant activated factor VII (rFVIIa, NovoSeven; Novo Nordisk A/S, Bagsværd, Denmark) in actively hemorrhaging trauma patients are limited. We present detailed safety data from a large multicenter, randomized, placebo-controlled phase III study (the CONTROL trial).

Methods: Data from 560 patients were analyzed. Subjects were monitored for adverse events (AEs) after rFVIIa or placebo administration. Incidences, timing, and presence of risk factors were reported by site investigators, supported by external study monitors and overseen by an independent Data Monitoring Committee.

Results: There were no differences in overall mortality, organ system failure, or AEs, serious AEs, or medical events of special interest. Arterial and venous thromboembolic (TE) events and their risk factors were similar in both groups. The greatest risk factor for TE events was a chest injury requiring mechanical ventilation >3 days (86%). There were four site investigator-reported myocardial infarctions in the rFVIIa group of which only one met diagnostic criteria preestablished by the Data Monitoring Committee. There were no reported myocardial infarctions in the placebo group. Troponins were increased in 30% of all patients. The rate of acute respiratory distress syndrome was lower in the rFVIIa (3.0%) than in the placebo (7.2%) group ($p = 0.022$).

Conclusions: This represents the largest placebo-controlled dataset of rFVIIa use in trauma patients to date. In this prospective study of critically bleeding trauma patients, rFVIIa use was associated with an imbalance of investigator-reported Acute myocardial infarction/non-ST segment elevation myocardial infarction (AMI/NSTEMI), but was not associated with an increased risk for other AEs, including TE complications.

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COMMENTARY

Hemorrhagic shock accounts for 30–40% of all acute deaths from trauma [1], and coagulopathy is a major contributor to this blood loss due to various reasons [2]. Since 1999, recombinant activated Factor VII (rFVIIa) has been used "off-label" in the management of trauma-associated coagulopathy [3].

The original CONTROL trial was a randomized double-blinded multi-center prospective study. To our knowledge, this is the largest trial to date designed to test, primarily, the efficacy and safety of rFVIIa in the management of refractory traumatic hemorrhage after blunt trauma. The endpoints were 30 days mortality, need for blood transfusions, multi-organ failure and serious adverse events (SAEs) within the first 90 days. Adverse events of special interest were defined as thromboembolic incidents, including myocardial infarction, stroke and pulmonary embolism. Originally, the study planned to recruit 1502 patients from 150 hospitals in 26 countries. However, this was halted early after recruiting only 573 patients due to an interim analysis which revealed a lower mortality rate than predicted in the treatment group versus the placebo group (11% vs. 27.5%). The unexpectedly lower death rate was explained by either the rigorous evidence based guidelines implemented during the study period, and/or the exclusion of severely multi-injured patients. As a result, the study was underpowered for efficacy [4,5].

This paper, however, is a report of the post hoc analysis of the available safety data of those (560 patients) from the trial; the authors compared the reported SAEs between the treatment and placebo groups. The conclusion was that the overall significant baseline risk of severely injured trauma patients for adverse events was not increased by the administration of rFVIIa, including thromboembolic events.

The limitations of this analysis were mainly in the following points; firstly, it was underpowered regarding efficacy as well as safety, these concerns were already discussed by the authors. Secondly, more evidence is accumulating that excessive crystalloid use during resuscitation is associated with poor outcome after hemorrhage; this has been elaborated in a recent study which showed that crystalloid resuscitation in a ratio greater than 1.5:1 per unit of packed red cells transfused was independently associated with a higher risk of multi-organ failure and adult respiratory distress syndrome [6]. This was not addressed in the original CONTROL design. Adjusting for this variable may have changed the result, especially when the analysis of the CONTROL trial shows a statistically significant higher ARDS rate in the placebo group in comparison to the rFVIIa group.

CONCLUSION

In trauma patients, the safety of rFVIIa was not established in this study; and its usage will continue to be "off label" as a salvage therapy in exsanguinating patients.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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