Letter: Tranexamic Acid and Severe Traumatic Brain Injury: The Futile Search for Causality?

To the Editor:

Tranexamic acid (TXA) is the go-to antifibrinolytic agent for intraoperative situations where heavy bleeding is encountered. Having been around for some time, it has been tried and tested in various studies, with mixed results. Aside from the backdrop of fuzzy evidence, its purported mechanistic effect lingers on in the minds of clinicians and prompts its prevalent use in various trauma and surgery settings. For severe traumatic brain injury (TBI), the evidence is even scarcer. The CRASH-3 pragmatic trial[1] showed the benefit of early administration of TXA in a prespecified sensitivity analysis, which excluded the most severe TBI patients. A smaller trial, on 966 patients, showed a small and uncertain effect of TXA administration in moderate and severe TBI on mortality and 6-mo functional outcome.[2] A recent meta-analysis on 9 randomized controlled trials (RCTs) and 14 846 patients[3] demonstrated no statistically significant differences between patients treated with TXA and placebo groups in terms of mortality, long-term outcome, or hematoma expansion. This meta-analysis provides more robust evidence than the CRASH-3 trial and thus should take precedence to dictate clinical practice.

Very recently, a multicenter prospective observational study has been published, focusing solely on severe isolated TBI patients and their outcomes after TXA administration.[4] Evidence-generation in severe TBI remains notoriously difficult, and this article proves to be no exception to the rule.[5]

From the 2589 patients included, 719 composed the actual isolated severe TBI cohort. Of these, only 243 (34%) received TXA. There was a statistically significant association between TXA and 30-d mortality in the subgroup of isolated severe TBI patients, but no association for the entire cohort. The power analysis was calculated with the assumption that both groups would be of equal size, but this was not the case. The authors concluded that TXA use should be avoided in severe isolated TBI patients.

Pupillary reactivity was not reported in the baseline tables. It was accounted for, however, in the sensitivity analyses. Given the radical change in coefficients between the crude model and the model after multiple imputations, one could speculate that a large amount of the pupillary reactivity data was missing. The Glasgow Coma Scale (GCS) at baseline is the one registered upon arrival of first responders and used by the authors. GCS, especially the motor score, can change considerably from prehospital to study hospital.[6] GCS following resuscitation after arrival at a trauma center is the most reliable covariate associated with outcome.[6] Cranial imaging data were collected, according to the protocol, but not included in any of the models. The predicted baseline mortality for both groups (TXA and non-TXA) using validated models would have likely shown a higher predicted baseline mortality in the TXA group.[7] Confounding by indication is very difficult to account for in observational studies, especially for a heterogeneous disease such as TBI,[8] and is likely incompletely accounted for in this study. TXA was administered to patients with a clinical suspicion of TBI, based on the prehospital GCS. Helicopter emergency physicians might have systematically selected patients with the highest risk of mortality to receive the intervention in an effort to ensure TXA gets administered to actual severe TBI patients. The lack of data regarding the evolution of the patients included and of their intracranial hemorrhage (or lack thereof) and the lack of data regarding treatment make the study by Bossers et al[4] virtually impossible to use in order to enforce clinical decision-making.

Given these issues, and the magnitude of effect of missing data on the analyses, we also disagree with the authors' main conclusion. Severe isolated TBI patients constitute a subgroup in their study, and subgroup analyses should be regarded as exploratory and should not affect the main conclusion of the study, even in clinical trials, let alone in observational ones.[9]

TXA has, to date, no proven efficacy in severe TBI, despite a small subgroup analysis of the meta-analysis suggesting a decrease in hematoma expansion.[3] The most recent observational data published are laden with confounding by indication. Until more robust evidence is available, the effect of TXA in severe TBI remains unanswered. The most important subgroup that still needs to be investigated is represented by severe TBI patients with intracranial hemorrhage, especially post-traumatic intracerebral hemorrhage (contusions). If an effect is to be expected, this group will most likely be the one to benefit from it.

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