Tranexamic acid in traumatic brain injury: systematic review and meta-analysis trumps a large clinical trial?

Maas, A.I.R.; Steyerberg, E.W.; Citerio, G.

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EDITORIAL

Tranexamic acid in traumatic brain injury: systematic review and meta-analysis trumps a large clinical trial?

Andrew I. R. Maas[1*], Ewout W. Steyerberg[2,3] and Giuseppe Citerio[4]

Tranexamic acid (TXA) is a cheap, old antifibrinolytic agent that has been extensively tested in several settings where bleeding is a concern, including trauma and surgery, with variable results. In severely injured patients, when administered within the first 3 h following injury, TXA reduces overall mortality and death due to bleeding. The evidence in acute traumatic brain injury (TBI) is uncertain.

In this issue of Intensive Care Medicine, Al Lawati et al. [1] present a well conducted, state-of the art systematic review (SR) and meta-analysis on the efficacy and safety of tranexamic acid (TXA) in acute TBI. They included nine RCTs that enrolled 14,846 patients. No statistically significant differences were found between patients treated with TXA and placebo groups for mortality, long term outcome, hematoma expansion and risk of adverse events. This is a somewhat different conclusion than the trumpeted interpretation of the CRASH-3 trial collaborators on the results of their large pragmatic RCT on TXA in TBI [2]. Only small differences were reported in CRASH-3 between the TXA and placebo groups in the primary efficacy analysis. Emphasis was placed on a pre-specified sensitivity analysis that excluded the most severe patients. This secondary analysis showed a marginally significant reduction in number of head-injury related deaths ($n=40$ in 7637 patients) between the TXA and placebo groups (RR 0.89; 95% CI 0.80–1.00). Their interpretation that "treatment within 3 h of injury reduces head-injury related death" was broadly picked up by the media and many clinicians across the world have now included the early use of TXA in the treatment of TBI. Caution against this media hype was expressed in an editorial published in this journal [3]. Only an uncertain and small benefit of early administration of TXA was found in a recent RCT on the effect of out-of-hospital administration of TXA on 6-month functional outcome in 966 patients with moderate or severe TBI [4].

Al Lawati et al. [1] are careful in formulating their conclusions, stating only that results do not support strong directives, either for giving TXA, or against giving TXA. This diplomatic phrasing is likely induced by the impact of the CRASH-3 trial results on clinical practice. The evidence-based pyramid positions systematic reviews and meta-analysis at the top the pyramid (Fig. 1) and the findings of a SR and meta-analysis override those of a large clinical trial [5]. In this case, however, the overall effect sizes for all-cause mortality in the current meta-analysis and in CRASH-3 were very similar (RR 0.95; CI 0.88–1.02 vs. 0.96; CI 0.88–1.04). This may not be surprising as the main driver of the meta-analysis is the large CRASH-3 trial, with a weight of 89% for the analysis of mortality. As a consequence, the added value of the current meta-analysis over that of the CRASH-3 study is limited. This also holds for a previously published SR and meta-analysis [6], not cited by the authors, that reported similar results (RR for mortality 0.93; 95% CI 0.86–1.01). A strength of meta-analysis is that it has more statistical power in subgroup analyses. Various subgroup and sensitivity analyses are reported, but not differentiated for injury severity, as few trials reported separate outcomes for these subgroups. We suggest that meta-analysis of individual patient data across the trials be considered, for further subgroup analyses. In particular, CRASH-3 reported

*Correspondence: andrew.maas@uza.be
[1] Department of Neurosurgery, Antwerp University Hospital and University of Antwerp, Wilrijkstraat 10, 2650 Edegem, Belgium
Full author information is available at the end of the article

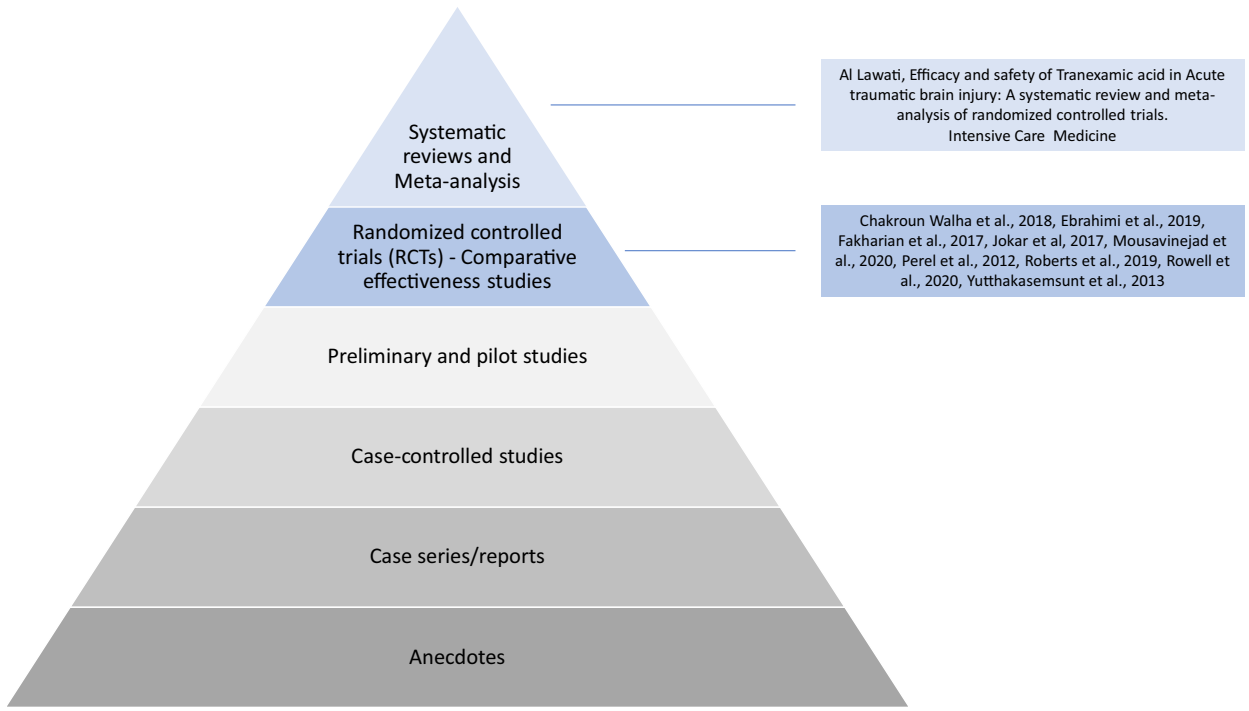

Fig. 1 The evidence-based pyramid positions systematic reviews and meta-analysis, as the Al Lawati one published in this issue of ICM, at the top the pyramid (here listed the nine RCTs included in the Al Lawati SR and meta-analysis) [5]

a reduction in deaths in patients with mild and moderate TBI (RR 0.78 95% CI 0.64–0.95), but not in patients with severe TBI (RR 0.99 CI 0.91–1.07). The mechanism for this differential effect is hard to understand. The purported mechanism of action of TXA is that it reduces bleeding by inhibiting plasmin production and preventing fibrin degradation. One would expect this to be more relevant in patients with severe TBI than in those with mild to moderate TBI. Unfortunately, CRASH-3 did not evaluate hematoma progression. In the meta-analysis of 3 studies including 1360 patients, TXA administration was found to reduce hematoma expansion (RR 0.77 95% CI 0.58–1.03). However, the evidence was of low quality and the difference in expansion (− 2.5 ml 95% CI − 6.5 ml to 1.6 ml) found in two other studies likely too small to translate into reduced mortality. Alternatively, a direct neuroprotective effect of TXA may be postulated, but this remains as yet hypothetical.

A difference existed in the approach to mortality analysis between this SR and the analysis reported by the CRASH-3 collaborators: The SR analyzed all-cause mortality, whilst the CRASH-3 used "head injury related death", a definition that may be prone to information bias. Furthermore, effects of TXA on functional outcome were meta-analyzed by performing a continuous analysis of outcome assessed by the Disability Rating Scale (DRS) (2 studies) and a dichotomized analysis of the Glasgow Outcome Scale (GOS) (5 studies). The choice for a continuous analysis of DRS and a dichotomous analysis of GOS was likely driven by available data but can be criticized. The DRS consists of four components (Arousal/awareness, Cognitive ability to handle self-care functions, Physical dependence and Psychosocial adaptability) with a combined score ranging from 0 to 29. It is, however, not an interval scale, and probably not even ordinal.

Good practice should be guided by evidence. This SR and meta-analysis provide the best possible evidence, not supporting the use of TXA for improving mortality or functional outcome of TBI. Neither, does it prove the absence of effect. A statement such as "pooled analysis found that TXA likely had no effect on mortality (RR 0.95; 95% CI, 0.88–1.02)" is hence incorrect. The inclusion of the value 1 in the 95% confidence interval implies that the effect is statistically non-significant but does not exclude a small effect size. Proving absence of effect is perhaps even more difficult than proving benefit. Indeed, the trial sequential analysis as reported confirmed that the information size was not enough to exclude an effect of the intervention, with over 25,000 patients required for an anticipated relative risk reduction of 10%. Therefore, only a super megatrial could solve this conundrum. The

question is if proving absence of benefit, or, at most only a minimal benefit should motivate such a large study.

Drawing definitive conclusions in this situation is hard. This SR confirmed no safety issues in patients with TBI. Consequently, there is no contra-indication for treating patients with polytrauma and concomitant TBI with TXA according to general trauma recommendations. Quoting Hippocrates, "as to diseases, make a habit of two things: to help, or at least, to do no harm" (Epidemics, Book I, Ch. 2).

In patients with isolated TBI, however, current evidence may be insufficient to warrant routine administration of TXA, as benefits–if present–are small and the mechanistic effect in patients with mild and moderate TBI–the subgroup with benefit in CRASH-3–insufficiently explained.

Author details
[1] Department of Neurosurgery, Antwerp University Hospital and University of Antwerp, Wilrijkstraat 10, 2650 Edegem, Belgium. [2] Department of Biomedical Data Sciences, Leiden University Medical Center, Leiden, The Netherlands. [3] Center for Medical Decision Sciences, Department of Public Health, Erasmus MC–University Medical Center Rotterdam, Rotterdam, The Netherlands. [4] School of Medicine and Surgery, University of Milano - Bicocca, Monza, Italy.

Compliance with ethical standards

Conflicts of interest
The authors report no relevant conflicts of interest.

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