Defending tranexamic acid and sensible scientific clinical trial design

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Three recent clinical trial reports published in the *New England Journal of Medicine* (NEJM) appear to undermine reputed effectiveness of tranexamic acid (TXA) as a hemostatic drug. They found no value for TXA over placebo as they used TXA, and as they assessed the outcome.

TXA is not magic. It is a lysine analogue that binds on and off to circulating and clot-attached plasminogen, preventing plasminogen from binding to the fibrin clot's lysines and thereafter lysing the clot.[1] There is plenty of circulating plasminogen, 200 mg/l of blood, and 5 liters of blood, so about 1g. TXA has a short half-life in plasma, 2 hours, so it is generally given as a 1g loading dose, then 1g over 8 hours, continuously until bleeding is controlled.

The most recent NEJM report, of a single dose of 1g TXA immediately preoperatively prior to Caesarean section, measured need for transfusion or death within 7 days or by discharge.[2] It found an absolute risk reduction of only 0.6% for TXA and reported an incorrect two-sided p-value of 0.19. The accurate p-values by a variety of techniques are 0.09 to 0.10. Since the hypothesis was TXA would help, a one-sided p-value would have been more appropriate. Most important, a single 1g bolus of TXA is going to have very limited benefit after its concentration plummets via urinary excretion. There was a small significant reduction (16% *vs* 18%) in the need for intervention addressing bleeding within 7days: perhaps due to better intraoperative hemostasis? Regardless, for a hemostatic drug with a 2 hours elimination half-life, don't expect other than early benefit (early blood loss wasn't reported) over a lengthy 7days.

A different NEJM report compared 1g TXA to placebo at the start and again at the end of non-cardiac surgery.[3] This time, the outcome was important bleeding within 30 days, as though TXA in such patients had extraordinary staying power. Here, even the 2-sided p-value was <0.001, there was a tight 95% CI around an absolute risk reduction of 2.6% (over 30 days, with just 2 doses on day 1). The Kaplan-Meier curves show all the benefit was early. There was significantly less major bleeding and fewer transfusions in the TXA group and no safety concerns. Yet the authors concluded *non-inferiority of TXA was not established* because of their unusual inexplicable hypothesis-testing.

A third NEJM report of severe trauma patients compared placebo to 1g TXA pre-admission and 1g infused over 8 hours.[4] But excitement about correct application of simple pharmacology and clinical trial design ended there. The outcome was functional outcome at 6 months, and there was no difference. Yes, 8 hours of those little lysine analogue molecules couldn't repair all the internal injuries and clinical lapses over six months, and the behavioral quirks that might have led to the major trauma in the first place. There were significant TXA group reductions in death at 24 hours, 30 days, and death due to bleeding, but TXA could not do the heavy lifting required to change the patient function trajectories at the 6-month mark. So it failed; the conclusion was TXA *did not result in a greater number of patients surviving with a favorable functional outcome at 6 months than placebo.*

However, bold NEJM editorialists provided a ray of hope:

> *The PATCH-Trauma trial investigators did not specify the hypothesized mechanism by which tranexamic acid might reduce disability, but in this group of severely injured patients, it would not be surprising if patients saved by tranexamic acid treatment were disabled. A patient with an exsanguinating pelvic injury who survives because of tranexamic acid treatment still has a potentially disabling pelvic injury… But is less than full recovery at 6 months or even longer without value? It is hard to imagine that doctors or paramedics would withhold a treatment that saves lives in the short-term because survivors may be severely disabled at 6 months.*

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Emphasizing that TXA is not magic, it did not prevent blindly-adjudicated hemorrhage deaths in gastrointestinal bleeding that was 75% variceal (esophageal or gastric), where 54% of deaths occurred on day 1.[6] Variceal bleeding often requires procedures and is difficult to control. At least these investigators gave a proper bolus and 24h infusion. There was a slight increase in thrombosis and seizures in the TXA group in these patients with unreported renal function.

From these three pharmacokinetic and clinical trial mishaps and a useful study we can learn where TXA can be effective, not in variceal bleeding, and that we must give it continuously, similarly to constant infusion vasopressor therapy. We can learn that large groups of prominent investigators will pick overtly strange outcomes far distant in time from when the TXA could possibly have effect, dependent upon many factors other than TXA's short-term reversible inhibition of plasminogen. We can learn that NEJM editors will publish such strange reports and that there are the rare brave sensible expert editorialists who will politely challenge them.

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