Tranexamic Acid Effects in Trauma Patients with Significant Hemorrhage

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The term *evidence-based medicine* was first coined by Sackett and colleagues[1] as "the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients." The key to practicing evidence-based medicine is applying the best current knowledge to decisions in individual patients. Medical knowledge is continually and rapidly expanding, and it is impossible for an individual clinician to read all the medical literature. For clinicians to practice evidence-based medicine, they must have the skills to read and interpret the medical literature so that they can determine the validity, reliability, credibility, and utility of individual articles. These skills are known as critical appraisal skills. Generally, critical appraisal requires that the clinician have some knowledge of biostatistics, clinical epidemiology, decision analysis, and economics as well as clinical knowledge.

The Canadian Association of General Surgeons (CAGS) and the American College of Surgeons (ACS) jointly sponsor a program titled "Evidence-Based Reviews in Surgery" (EBRS), supported by an educational grant from Ethicon Inc and Ethicon Endo Surgery Inc. The primary objective of this initiative is to help practicing surgeons improve their critical appraisal skills. During the academic year, 8 clinical articles are chosen for review and discussion. They are selected not only for their clinical relevance to general surgeons, but also because they cover a spectrum of issues important to surgeons; for example, causation or risk factors for disease, natural history or prognosis of disease, how to quantify disease (measurement issues), diagnostic tests and the diagnosis of disease, and the effectiveness of treatment. Both methodologic and clinical reviews of the article are performed by experts in the relevant areas and posted on the EBRS website. A listserve discussion is held where participants can discuss the monthly article. Fellows and candidates of the College can access Evidence-Based Reviews in Surgery through the American College of Surgeons website (www.facs.org). All journal articles and reviews are available electronically through the website. Currently we have a library of 50 articles and reviews, which can be accessed at any time. Each October, a new set of articles will be available each month until May. Surgeons who participate in the current (modules) packages can receive CME credits by completing a series of multiple choice questions. Additional information about EBRS is on the ACS website or by email to the administrator, Marg McKenzie at mmckenzie@mtsinai.on.ca.

In addition to making the reviews available through the ACS and CAGS websites, 4 of the reviews are published in condensed versions in the *Canadian Journal of Surgery*, 4 in the *Journal of the American College of Surgeons*, and 4 in *Diseases of Colon and Rectum* each year.

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SELECTED ARTICLE

Effects of Tranexamic Acid on Death, Vascular Occlusive Events and Blood Transfusion in Trauma Patients with Significant Haemorrhage (CRASH-2): A Randomized Placebo-Controlled Trial

CRASH-S Trial Collaborators. Lancet 2010;376:23–32.

Question: Does early administration of tranexamic acid affect mortality within 4 weeks of injury in patients with or at risk of significant bleeding?

Design: Randomized controlled trial

Setting: Multicenter trial that included 274 hospitals in 40 countries

Patients: Twenty thousand two hundred eleven trauma patients with or at risk of significant bleeding were randomly assigned within 8 hours of injury to either tranexamic acid or placebo.

Intervention: Patients allocated to tranexamic acid received a loading dose of 1 g tranexamic acid infused over 10 minutes followed by an infusion of 1 g over 8 hours.

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Main outcome: Death in hospital within 4 weeks of injury.

Results: All cause mortality was significantly reduced in the tranexamic acid group (1,463[14.5%] compared with the placebo group 1,613 [16.0%]; relative risk 0.91, 95% CI 0.85–097; p = 0.0035). Similarly the risk of death due to bleeding was significantly reduced (489 [4.9%] vs 574 [5.7%]; relative risk 0.85, 95% CI 0.76–0.96; p = 0.0077).

Conclusion: Tranexamic acid safely reduced the risk of death in bleeding trauma patients. Therefore, tranexamic acid should be considered for use in bleeding trauma patients.

Commentary: The basic clinical question that was studied in this study was whether the early administration of a 1 g of tranexamic acid over 10 minutes (loading) followed by 1 g over 8 hours (infusion) compared with placebo affected mortality within 4 weeks of injury in patients with, or at risk of, significant bleeding. [1] There is evidence that tranexamic acid an antifibrinolytic agent, is effective in stopping bleeding. Indeed, it has been used selectively in cardiac surgery,[2-4] neurosurgery,[4] and orthopaedics[5], with positive results, therefore providing the rationale to explore the utility of this cheap and safe drug in trauma patients.

The investigators randomized 20,211 trauma patients admitted to 274 hospitals located in 40 countries on 6 continents to tranexamic acid or placebo. Although this is a broad sample, it is noteworthy that fewer than 2% of the patients were recruited in countries such as the United States, Canada, Australia, New Zealand, UK or Western Europe, where considerable investment in trauma systems, access to early intervention, and supply of blood products may have led to differences in treatment compared with that received by most patients enrolled in CRASH-2. Trauma patients considered to be at risk of bleeding, as indicated by as little as a single systolic blood pressure reading of less than 100 mmHg or a heart rate of more than 100 beats/minute (neither of which is specific for bleeding) were eligible for inclusion. The intervention group received 1 g of tranexamic acid on arrival at the trauma center and 1 g over the next 8 hours. The control group received an identical-looking placebo. The primary outcome of the CRASH-2 trial was in-hospital death within 4 weeks of injury. Secondary outcomes were need for transfusion, surgical interventions, and vascular occlusive events. This trial was the near epitome of the large simple, austere trial design. Although the data collected were austere, they included outcomes and relative safety measures, but did not assess clinically relevant mechanisms, and relied on clinical impression for complications such as venous thrombosis. All patients enrolled in the trial were accounted for. Out of 20,211 patients enrolled, 4 were omitted because consent was withdrawn after randomization, and 80 patients had incomplete follow-up data, leaving 20,127 patients in the analysis.

Although conceptualized as a study assessing the hemostatic effects of tranexamic acid, the design and subsequent patient enrolment ultimately resulted in a very large study that included a worldwide cohort of variably injured patients with varying blood loss and requirements for interventions. Nonetheless, the relative risk (RR) of death in the tranexamic acid group was 0.91 (95% CI 0.85–0.97), without a significant increase in vascular occlusive events. Mortality risk was reduced from 16.0 to 14.5% (RR 0.91, 95% CI 0.85–0.97; p = 0.0035). Although the treatment and control groups had similar blood transfusion requirements, the relative risk of death due to bleeding (as judged by the clinician) was 0.85 (95% CI 0.76–0.96), with an absolute risk reduction from 5.7% to 4.9%. A subsequent analysis showed a strong temporal effect with death due to bleeding; if given less than 1 hour after injury the RR was 0.68 (95% CI 0.57–0.82), 1 to 3 hours after injury the RR was 0.79 (95% CI 0.64–0.97), and more than 3 hours after injury tranexamic acid appeared to be harmful – a concern that should be well noted by all (RR 1.44, 95% CI 1.12–1.84). Why this is the case was unclear, particularly because the actual effect of tranexamic acid on coagulation and inflammatory parameters was not assessed. The necessarily austere study design prevented the analysis of the effect of Injury Severity Scores, acid base results, or laboratory measures of coagulation, including fibrinolysis, on outcomes.

Overall, this study represents a tremendous effort, and illustrates that worldwide collaboration is possible, if a protocol is simple, easy to understand and conduct and investigators are motivated. Although the trial has left unanswered scientific questions, such as the mechanism of action, for example, its sheer size renders it a landmark trial that supports the careful introduction of this drug into greater clinical usage within the 3-hour time window. Subsequent studies have estimated the incremental cost per life saved as varying from $48 to $64, depending on the income class of the country.[6] Moving forward, it is certain that much more effort will be invested to understand the role and mechanisms of tranexamic acid in acute trauma resuscitation. In this regard, a recent observational study examining its effect in military trauma alongside other components of damage control resuscitation has been reassuring.[7]

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