Systematic Review Snapshot
Clinical Synopsis

TAKE-HOME MESSAGE

The use of tranexamic acid may reduce the risk of death in bleeding trauma patients.

METHODS

DATA SOURCES

In July 2010, the authors searched the Cochrane Injuries Group's specialized register, Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, Science Citation Index, National Research Register, Zetoc, SGILE, Global Health, LILACS, and Current Controlled Trials.

STUDY SELECTION

All randomized controlled trials of the administration of antifibrinolytic agents (aprotinin, tranexamic acid, and ε-aminocaproic acid) to patients of any age with acute traumatic injury.

DATA EXTRACTION AND SYNTHESIS

Two independent authors reviewed all titles and abstracts and identified those that met a specific set of inclusion criteria. Data were pooled from randomized controlled trials comparing tranexamic acid, aprotinin, or ε-aminocaproic acid with placebo, with the primary outcome of mortality. Two authors assessed the quality of the individual trials, and disagreements were resolved by consensus. Information on loss to follow-up, the use of blinding, and intention to treat was extracted.

Does the Administration of Antifibrinolytic Drugs in Acute Trauma Reduce Mortality?

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Results

Outcomes in patients treated with tranexamic acid versus placebo.[1]

Outcome	Relative Risk (95% CI)	Number Needed to Treat
All-cause mortality	0.90 (0.85–0.97)	68
Death caused by bleeding*	0.85 (0.76–0.96)	NA
Vascular occlusive events*	0.84 (0.68–1.02)	NA

NA, Not applicable.
*Based on data only from the CRASH-2 trial.

Only 2 trials (N=20,451) were included that compared tranexamic acid with placebo. The Clinical Randomization of an Antifibrinolytic in Significant Hemorrhage 2 (CRASH-2) trial comprised the majority of the patients (N=20,211) and was responsible for 99% of the weighted effect estimate. In this large multinational study, trauma patients older than 16 years and presenting within 8 hours of injury with significant hemorrhage (systolic blood pressure <90 mm Hg, pulse rate >110 beats/min, or both) or considered to be at risk of significant hemorrhage were eligible for the trial. Tranexamic acid was administered intravenously as a loading dose of 1 g over 10 minutes, followed by an intravenous infusion of 1 g over 8 hours.[1] The risk of bias was graded as low for the large CRASH-2 trial, but the risk of bias in the smaller trial by Yutthakasemsunt et al[2] (N=240) was unclear because data were available only from an abstract when the Cochrane review was conducted.

The authors estimated a 10% relative risk reduction for mortality without an increased risk of vascular occlusive events or increased need for blood products or surgical intervention; the absolute risk reduction in the large CRASH-2 trail was approximately 1.5%, with an estimated number needed to treat of 68.

Only 2 older trials compared the effects of aprotinin versus placebo. Auer et al[3] randomized 20 subjects and then enrolled an additional 5 patients to the aprotinin group; it was not possible to separate the nonrandomized patient data from the randomized data. McMichan et al[4] performed a randomized controlled trial including 77 patients that demonstrated no difference in mortality between aprotinin and placebo. Aprotinin was removed from the US market in 2007 because of safety concerns.[5]

Commentary

Trauma is a leading cause of death worldwide, with approximately 4 million deaths annually.[6] Tranexamic acid is inexpensive and easy to use and, when given early, may reduce mortality. According to the British National Formulary in 2009, a gram of tranexamic acid costs

Summary of FDA Information on Tranexamic Acid*

Indications

Patients with hemophilia for short-term use (2 to 8 days) to reduce or prevent hemorrhage and reduce the need for replacement therapy during and after tooth extraction.

Contraindications

Patients with subarachnoid hemorrhage, active intravascular clotting, or a known hypersensitivity to tranexamic acid. It should also not be used for patients with acquired defective color vision because this is a method of evaluating tranexamic acid toxicity. No retinal changes have been observed in patients treated with tranexamic acid, but visual abnormalities are the most common adverse reaction reported in Sweden, and regular ophthalmologic examinations are recommended during treatment.

*For a full monograph of tranexamic acid from the FDA, see http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.DrugDetails.

$5.70. The CRASH-2 collaborators published a cost-effectiveness analysis showing that the administration of tranexamic acid is cost-effective across low-, middle-, and high-income countries.[7] A recent *Lancet* article from the CRASH-2 collaborators concludes that the benefits of tranexamic acid are observed only when the drug is administered in the first 3 hours after trauma.[8] Although the results from these 2 trials are promising, most of the data come from 1 large study that enrolled most of the subjects in developing countries, so the applicability to North America is uncertain; tranexamic acid has not been approved by the Food and Drug Administration (FDA) for treatment of traumatic injury (Figure).[9] The authors of the Cochrane review were also the authors of the CRASH-2 study, so there may exist some intellectual conflict of interest.

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