Tranexamic Acid for Upper Gastrointestinal Bleeding

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The NNT color recommendation	Yellow
Summary heading	Tranexamic acid may improve survival in upper gastrointestinal bleeding.
Benefits in NNT	1 in 30 were helped (death prevented) when compared to placebo; no one was helped when compared against antiulcer therapy
Benefits in percentages	3.5% were helped (death prevented) when compared to placebo; no one was helped when compared against antiulcer therapy
Harms in NNT (NNH)	No one was harmed
Harms in percentages	No one was harmed
Efficacy endpoints	Death, rebleeding, and requirement for surgery
Harm endpoints	Thromboembolic events, myocardial infarction, pulmonary embolism, cerebral infarction, or deep vein thrombosis
Who was in the studies	1,701 patients from eight randomized controlled trials with acute upper gastrointestinal bleeding

NARRATIVE

Upper gastrointestinal bleeding is common and accounts for at least half of the nearly 500,000 annual U.S. hospitalizations for gastrointestinal bleeding.[1] In the acute setting, severe bleeding is treated with intravenous fluids, blood products, antiulcer therapy, and hemostasis by endoscopy.[2] Tranexamic acid (TXA) is an antifibrinolytic agent shown to reduce bleeding.[3,4] TXA has been proven to be effective in improving patient-centered outcomes after severe hemorrhage due to trauma.[5] The authors of this systematic review sought to evaluate the benefit of TXA administration specifically for upper gastrointestinal bleeding.

The systematic review summarized here[6] identified eight randomized trials of TXA in 1,701 subjects presenting with acute upper gastrointestinal bleeding among patients admitted to the hospital, including some in the intensive care unit. Two comparisons were made: TXA versus placebo and TXA versus antiulcer therapy (cimetidine or lansoprazole). Primary outcomes were mortality and adverse events. Compared to placebo, TXA reduced mortality (relative risk [RR] = 0.60, 95% CI = 0.42 to 0.87, ARR = 3.5%, NNT = 30, moderate-quality evidence). However, because of a high attrition in several trials the results must be interpreted with caution. About 20% of the studied patients were withdrawn or excluded for reasons such as lack of confirmation of the presence of bleeding, presence of malignancy, terminal illness, or late administration of treatments. Reanalysis including all participants and considering missing patients as treatment failures did not show mortality benefit.[5]

In the second comparison, TXA versus antiulcer therapy (cimetidine or lansoprazole), only two trials were included, and no mortality benefit was found. Administration of TXA did not reduce the risk of rebleeding (RR = 0.72, 95% CI = 0.50 to 1.03, low-

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quality evidence) or blood transfusion (RR = 1.02, 95% CI = 0.94 to 1.11, very-low-quality evidence).

Although meta-analysis could not be performed for harm endpoints due to lack of adverse event reporting for all trials, three studies did include data on thromboembolic events. There was no difference between the TXA and placebo groups in combined serious thromboembolic events (myocardial infarction, pulmonary embolism, and cerebral infarction; RR = 1.37, 95% CI = 0.36 to 5.28), nor did TXA increase the risk of deep vein thrombosis (RR = 2.32, 95% CI = 0.60 to 8.89).

CAVEATS

The authors of this Cochrane review judged the available evidence to be of moderate to low quality, largely due to the risk of bias and clinical heterogeneity among included trials. Notably, the trials were conducted over nearly four decades (from 1973 to 2011), with six of eight published between 1973 and 1987, likely accounting for much of the heterogeneity. A high dropout rate was also concerning. When this was accounted for (in a worst-case scenario), the mortality benefit was not significant. The included trials also used different doses and routes of administration for TXA and were mostly performed 30 to 45 years ago. Management patterns, hemostatic technology, and cointerventions have since changed, in some cases dramatically, making applicability to current practice questionable. Finally, all trials enrolled admitted patients. Previous trials have shown that TXA is most efficacious when administered early (within 1 hour).[5] Therefore, the delay in administration of TXA might have reduced efficacy, further reducing applicability and generalizability for ED patients.

We have assigned a color recommendation of yellow (unclear benefits) to this intervention. Limitations of the reported data, particularly the lost to follow-up and dropout rates, the high risk of bias, and the presence of significant heterogeneity justify this rating. A large pragmatic double-blind controlled trial with a target sample size of 12,000 subjects is currently ongoing.[7] We are hopeful this trial will provide better evidence. Despite TXA's lack of demonstrated benefit compared to standard treatments with respect to the endpoints of mortality or rebleeding, given the relative safety, lack of significant adverse events, and low cost of the medication, it may be reasonable to consider TXA in severe upper gastrointestinal bleeding as an adjunct to standard therapy or if standard therapy fails.

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