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Cochrane in *CORR*®: Topical Application of Tranexamic Acid for the Reduction of Bleeding (Review)

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Importance of the Topic

Many orthopaedic procedures are associated with substantial perioperative blood loss, which is associated with complications, increased length of stay, and even death [9]. Although blood transfusions generally are safe, they can cause transfusion reactions and, rarely, the transmission of infectious diseases.

Tranexamic acid is an amino acid derivative that inhibits fibrinolysis [7]. More than 100 randomized controlled trials have demonstrated that intravenous tranexamic acid for surgical patients reduces the risk of receiving a blood transfusion by about one-third, but potential harms of systemic administration include pulmonary embolism, stroke, and myocardial infarction, each of which could be fatal [8]. Therefore, considerable research has recently focused on whether topical administration might offer similar efficacy with acceptable safety.

In this meta-analysis of 29 randomized controlled trials involving 2612 participants, topical tranexamic acid decreased bleeding by 29% (relative risk [RR], 0.71; 95% confidence interval [CI], 0.69–0.72) and the need for blood transfusions by 45% (RR, 0.55; 95% CI, 0.46–0.65) but the study could draw no firm conclusions about the risks for harmful thromboembolic events [7]. Although just 10 of the trials involved total hip or knee arthroplasty and two

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(Ker K, Beecher D, Roberts I. Topical application of tranexamic acid for the reduction of bleeding. Cochrane Database of Systematic Reviews 2013, Issue 7. Art. No.: CD010562. DOI: 10.1002/14651858.CD010562.pub2.)

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involved spine surgery (the remaining trials involved cardiac surgery, dental surgery, or other specialties), orthopaedic surgeons can be reassured that this meta-analysis is generalizable to their practice settings because the main findings were consistent across orthopaedic and nonorthopaedic trials.

Upon Closer Inspection

Allocation concealment refers to the extent to which those individuals responsible for enrolling patients were unaware of, and could not influence, the study arms to which patients were assigned. Allocation concealment is particularly important because trials with inadequate methods are prone to selection bias and systematically overestimating treatment effects [11]. Sealed opaque envelopes are often used to maintain concealment, but they are vulnerable to tampering and less secure than remote internet- or telephone-based systems [12]. The pooled reduction in risk for blood transfusion was slightly less impressive when trials with high-risk or unclear methods of allocation concealment were excluded (33% decreased risk of receiving a transfusion, [RR, 0.67; 95% CI, 0.54–0.84]), but clinicians can be more confident that this result approximates the truth because it is at less risk of selection bias.

Despite pooling data from 2612 participants, this meta-analysis was still underpowered by at least an order of magnitude (or more) to reliably inform about the risks for potential thromboembolic harms such as pulmonary embolism, stroke, and myocardial infarction—because most of these events are rare to begin with. For example, according to conventional power calculations, approximately 50,000 patients would be required to detect a 25% relative risk reduction for events that occur less than 1% of the time [4]. Therefore, readers should remain cautious when balancing the observed benefits of topical tranexamic acid against potential harms. Current best evidence comes from a nonrandomized retrospective database study of 872,416 patients who underwent total hip or knee arthroplasty, which did not find any increased rates of thromboembolic harms or mortality [10].

Take-home Messages

Several expert panel consensus statements have endorsed routine use of topical tranexamic acid for hip and knee arthroplasty, but there are currently no major guideline recommendations for orthopaedic surgeons [2, 6]. In order to determine the direction and strength of a recommendation, guidelines panels should integrate confidence in the pooled effect estimates, the balance of desirable and undesirable outcomes among alternative management strategies, the values and preferences of typical patients, and the potential use of healthcare resources [1]. Given residual uncertainty about the risks for harm and potential variability in patients' preferences about trading off these risks against bleeding and blood transfusions, strong general recommendations may not be warranted. However, current economic analyses suggest that topical tranexamic acid is likely to be cost-effective for procedures with higher risks for blood loss such as total hip and knee arthroplasty because it reduces costs related to blood transfusions and lengths of stay [5, 13].

The main findings of this meta-analysis have been confirmed in other meta-analyses that included additional trials for TKA, THA, and spine surgery, but several important questions remain unanswered [3, 14, 15]. For example, additional large observational studies are warranted to resolve uncertainty in the risks for thromboembolic harms, clarify whether certain dosing regimens might be superior to others, investigate use in specific patient populations such as those with contraindications to intravenous tranexamic acid, and investigate efficacy and cost-effectiveness in combination with other perioperative blood management strategies.

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Appendix

Topical application of tranexamic acid for the reduction of bleeding (Review)

Ker K, Beecher D, Roberts I

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DOI: 10.1002/14651858.CD010562.pub2.

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[Intervention Review]

Topical application of tranexamic acid for the reduction of bleeding

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ABSTRACT

Background

Intravenous tranexamic acid reduces bleeding in surgery, however, its effect on the risk of thromboembolic events is uncertain and an increased risk remains a theoretical concern. Because there is less systemic absorption following topical administration, the direct application of tranexamic acid to the bleeding surface has the potential to reduce bleeding with minimal systemic effects.

Objectives

To assess the effects of the topical administration of tranexamic acid in the control of bleeding.

Search methods

We searched the Cochrane Injuries Group Specialised Register; Cochrane Central Register of Controlled Trials (CENTRAL) in *The Cochrane Library;* Ovid MEDLINE®, Ovid MEDLINE® In-Process & Other Non-Indexed Citations, Ovid MEDLINE® Daily and Ovid OLDMEDLINE®; Embase Classic + Embase (OvidSP); PubMed and ISI Web of Science (including Science Citation Index Expanded and Social Science Citation Index (SCI-EXPANDED & CPCI-S)). We also searched online trials registers to identify ongoing or unpublished trials. The search was run on the 31st May 2013.

Selection criteria

Randomised controlled trials comparing topical tranexamic acid with no topical tranexamic acid or placebo in bleeding patients.

Data collection and analysis

Two authors examined the titles and abstracts of citations from the electronic databases for eligibility. Two authors extracted the data and assessed the risk of bias for each trial. Outcome measures of interest were blood loss, mortality, thromboembolic events (myocardial infarction, stroke, deep vein thrombosis and pulmonary embolism) and receipt of a blood transfusion.

Main results

We included 29 trials involving 2612 participants. Twenty-eight trials involved patients undergoing surgery and one trial involved patients with epistaxis (nosebleed). Tranexamic acid (TXA) reduced blood loss by 29% (pooled ratio 0.71, 95% confidence interval (CI) 0.69 to 0.72; P < 0.0001). There was uncertainty regarding the effect on death (risk ratio (RR) 0.28, 95% CI 0.06 to 1.34; P = 0.11), myocardial infarction (RR 0.33, 95% CI 0.04 to 3.08; P = 0.33), stroke (RR 0.33, 95% CI 0.01 to 7.96; P = 0.49), deep vein

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thrombosis (RR 0.69, 95% CI 0.31 to 1.57; P = 0.38) and pulmonary embolism (RR 0.52, 95% CI 0.09 to 3.15; P = 0.48). TXA reduced the risk of receiving a blood transfusion by a relative 45% (RR 0.55, 95% CI 0.55 to 0.46; P < 0.0001). There was substantial statistical heterogeneity between trials for the blood loss and blood transfusion outcomes.

Authors' conclusions

There is reliable evidence that topical application of tranexamic acid reduces bleeding and blood transfusion in surgical patients, however the effect on the risk of thromboembolic events is uncertain. The effects of topical tranexamic acid in patients with bleeding from non-surgical causes has yet to be reliably assessed. Further high-quality trials are warranted to resolve these uncertainties before topical tranexamic acid can be recommended for routine use.

PLAIN LANGUAGE SUMMARY

Topical treatment with a blood-clot promoting drug to reduce bleeding

Hundreds of thousands of people worldwide suffer ill health caused by severe bleeding. Tranexamic acid is a drug that helps blood to clot and so it could help people who are bleeding. We already know that giving tranexamic acid intravenously (directly into the vein) reduces bleeding in accident victims and in patients having operations. But some doctors don't always give it this way because they are worried that it might have bad side effects in certain patients, such as causing blood clots where they are not wanted. An alternative way to give this drug is to mix it with sterile water and apply it directly to the bleeding surface (this is known as 'topical' application). Because less of the drug might be absorbed into the body when it is given this way, it could be less likely to have bad side effects.

This review looked at trials assessing the effects of topical tranexamic acid in patients who are bleeding. Twenty-nine trials were found; 28 involved patients bleeding during operations and one involved people with nosebleeds. When the results of these trials were gathered together they showed that when tranexamic acid was given topically, it reduced the amount of blood that patients lost and made it less likely that they had a blood transfusion.

The authors of this review concluded that topical tranexamic acid reduces bleeding in patients who are having an operation. But because there are no trials, we are not sure if it also reduces bleeding from other causes, such as childbirth or bleeding from stomach ulcers.

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