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Topical use of tranexamic acid in cardiac surgery—A review and meta-analysis of four randomized controlled trials

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A B S T R A C T
The article deals with the issue of topical use of tranexamic acid in cardiac surgery. Four randomized, double-blind trials comparing tranexamic acid vs. placebo were identified in the available literature (371 patients in total). In all of these studies the topical application of tranexamic acid significantly reduced postoperative blood loss, whereas a significant reduction of transfusion requirements was only described in one of these studies. A meta-analytic approach confirmed a significant reduction in blood loss (in 24 h) by 321.6 mL on average (95% confidence interval = 530.3 mL, −112.9 mL; \( p = 0.003 \)). Another trial was performed to examine a possible augmentation of systemic administration of tranexamic acid by the additional topical application. Despite an evident tendency toward lower blood loss in the group treated also topically, the differences between groups in this study did not reach statistical significance. There is an apparent need for further controlled trials with larger groups of patients.

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1. Introduction

A history of preventive application of fibrinolytic inhibitors in cardiac surgery is older than 30 years. This pharmacological strategy is frequently used to reduce postoperative blood loss, transfusion requirements and the frequency of early surgical revisions for bleeding. In 2007/2008, based on the results of Karkouti et al. [1], Mangano et al. [2] and Fergusson et al. [3], the most effective antifibrinolytic agent – aprotinin – was suspended from the global pharmaceutical market and it is not currently used at all (with the exception of re-authorization for the use in coronary artery bypass grafting in Canada, September 2011).

lysine analogues (tranexamic acid, e-aminocaproic acid) are an important part of blood saving programs in many cardiac surgery centers [4] but the efficacy and safety profile of these drugs are broadly investigated and discussed. While e-aminocaproic acid is often applied in the US, the use of tranexamic acid is more common in Canada and Europe [5]. E-aminocaproic acid is not presently registered by the State Institute for Drug Control and permitted for use in the Czech Republic.

2. Tranexamic acid overview

Tranexamic acid – 4-(aminomethyl)cyclohexane-1-carboxylic acid – is a synthetic derivative of the amino acid lysine.

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The antifibrinolytic activity is a result of reversible binding to plasminogen which prevents its interaction with fibrin (Fig. 1). Generally, plasminogen binds to fibrin at a lysine binding site and is converted in the presence of tissue plasminogen activator to plasmin. Tranexamic acid blocks the lysine binding site and prevents access of plasminogen to fibrin molecules [6,7].

Tranexamic acid is used in a variety of surgical procedures, including cardiac surgery (both on-pump/off-pump), orthopedic surgery, liver transplantation, prostatectomy, dental surgery and gynecology. A large, randomized, double-blind multicenter CRASH-2 trial proved that tranexamic acid reduced all-cause mortality at 4 weeks and the death rate due to bleeding in trauma patients [8].

Tranexamic acid is generally well tolerated but some adverse events were reported, as well and it is necessary to take them into consideration in everyday clinical practice. Theoretically, due to the antifibrinolytic mechanism, there is a possibility of an increased risk of thromboembolic events (e.g. early graft closure in coronary artery bypass grafting, deep vein thrombosis, pulmonary embolism, myocardial and cerebral infarctions), but in practice these adverse events were reported quite rarely [9]. Another serious adverse event recently discussed in cardiac surgery seems to be a risk of postoperative convulsive seizures, associated particularly with high-dose regimens [10,11]. This epileptogenic effect of tranexamic acid may be explained by a similarity between its molecules and the molecules of γ-aminobutyric acid (Fig. 2), which leads to the occupancy of γ-aminobutyricA brain receptors [12].

### 3. Systemic use of tranexamic acid

The systemic application of tranexamic acid is the most common approach in cardiac surgery. According to the available literature, recommended dosages vary across countries and cardiac centers (loading intravenous dose 1–10 g, addition to the content of the cardiopulmonary bypass circuit prime 500–2500 mg, continuous infusion 200–1000 mg/h) [13].

### 4. Topical application of tranexamic acid

The topical/local application of tranexamic acid into the pericardial cavity is not so frequent in comparison with its systemic use. The rationale for the topical application is based on Tabuchi et al. [14] and Khalil et al. [15] findings that the local fibrinolytic activity in the pericardial cavity exceeds that in the systemic circulation. A human pericardium contains high levels of tissue plasminogen activator, which under normal/physiological conditions prevents the formation of adhesions and maintains the fluidity of the pericardial cavity.

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**Fig. 1 – Antifibrinolytic action of tranexamic acid. A – activation of fibrinolysis; B – inhibition of fibrinolysis. t-PA – tissue plasminogen activator. Reproduced from Dunn CJ, Goa KL: Tranexamic Acid. A Review of its Use in Surgery and Other Indications, Drugs 1999, 57(6):1005–1032, with permission from Springer International AG (© 1999. All rights reserved).**

**Fig. 2 – Structural formulas and space-filling models of tranexamic acid (TA) and γ-aminobutyric acid (GABA).**
cavity. Surgical tissue manipulations may enhance this local fibrinolytic activity.

We searched MEDLINE from 1995 to 2012 with the following keywords: “Cardiac surgical procedures”, “Postoperative bleeding”, “Antifibrinolytic agents”, “Tranexamic acid” and “Topical administration”. The studies were assessed independently by both authors according to the methodology proposed in the literature [16]. The criteria were as follows: randomization, double-blinding and allocation concealment. We identified four randomized, double-blind, controlled trials written in English comparing the topical application of tranexamic acid vs. placebo (Table 1) [17–20]. One study written in the Turkish language [21] was not included in the review and the subsequent meta-analysis because of not fulfilling the above mentioned inclusion criteria. Additionally, we found a meta-analysis evaluating the efficacy and safety of the topical application of fibrinolytic inhibitors (aprotinin, tranexamic acid) in cardiac surgery [22].

According to the trial protocols, a dose of tranexamic acid varying from 1 g to 2.5 g in 100–250 mL of normal saline (or just normal saline solution as a placebo) was poured into the pericardial cavity and spread over mediastinal tissues at the end of procedures prior to sternal closure. In all of these trials the topical application of tranexamic acid significantly reduced postoperative blood loss (in 24 h), but the tendency toward reduced transfusion requirements (packed red blood cells) reached statistical significance in only one study with the highest concentration of tranexamic acid in the study solution [18].

In our original research we tested a possible augmentation of systemic administration of tranexamic acid (1 g before skin incision and subsequently 400 mg/h, 0.5 g as a supplement to the content of crystalloid pump prime) by the additional topical application (group A: 250 mL of normal saline+tranexamic acid 2.5 g, placebo group B: 250 mL of normal saline) during heart valve surgery [23]. Although a continuous tendency toward lower blood loss in group A was evident (Table 2), no statistical significance was reached at any time points (4, 8, and 24 h postoperatively). Table 2 also suggests that in placebo group B there was greater variability in blood loss at all time points (leading to a statistically significant difference of variances 24 h postoperatively). No significant difference in postoperative transfusion of packed red blood cells was found, but the proportion of patients requiring fresh frozen plasma after the surgery was bigger in placebo group B (group A: n=21, group B: n=36, p=0.008).

5. Meta-analysis of the trials comparing the topical application of tranexamic acid vs. placebo

5.1 Methods and statistical analysis

The meta-analysis included the four above mentioned trials, comparing the topical application of tranexamic acid vs. placebo (n=371 patients in total) [17–20]. Our study [23] investigating a possible augmentation of systemic administration of tranexamic acid by the additional topical application was not included because of a different way of drug administration (systemic application of tranexamic acid in both – treated and control – groups).

The meta-analysis focused on two primary outcomes: 24 h postoperative chest tube drainage and the incidence of postoperative transfusion requirements (red blood cells). The random-effect model was used to estimate pooled treatment effects. The results are presented in the form of weighted mean differences (in case of blood loss) and risk ratios (in case of transfusion needs) with corresponding 95% confidence intervals (95% CI). The heterogeneity was quantified by the I² statistics [24]. The J² test for heterogeneity was used to assess whether observed differences in the study results are compatible with the chance variation alone. In one study [20], chest tube drainage was reported as median and minimum and maximum. To estimate the missing mean and standard deviation, the log-normal model was fitted via maximum likelihood based on the three available order statistics. Since the characteristics of variability (ranges) were only reported for the total blood loss (not for 24 h), the calculation was

| Table 1 – Characteristics of trials comparing topical tranexamic acid vs. placebo. |
|--------------------------------|----------------|----------------|----------------|----------------|----------------|
| Study                          | No. of treated patients | No. of control patients | Drug dose                  | Significant difference in cumulative blood loss (24 h) | Significant difference in postoperative transfusion requirements (PRBC) |
| De Bonis et al. [17]          | 20             | 20             | 1 g TA/100 mL saline     | +**              | NS               |
| Abd. Azm and Abdullah [18]    | 50             | 50             | 2 g TA/100 mL saline     | +****             | +****            |
| Baric et al. [19]             | 97             | 96             | 2.5 g TA/250 mL saline    | +******           | NS*              |
| Fawzy et al. [20]             | 19             | 19             | 1 g TA/100 mL saline     | +*               | NS               |

PRBC – packed red blood cells; TA – tranexamic acid.
* p < 0.04.
** p = 0.01.
**** p < 0.01.
***** p < 0.001.
* Comparison of three groups (aprotinin, n=100; tranexamic acid, n=97; placebo, n=96).
based on the total postoperative chest tube drainage, which did not differ much from that for 24 h.

A statistical analysis was performed by statistical software Stata, release 9.2 (Stata Corporation, College Station, TX). p-Values less than 0.05 indicated a statistically significant result.

In two studies the number of patients requiring transfusion of red blood cells was not reported [18,20] and the authors were contacted for more information, but no response was obtained. These two studies were therefore excluded from the part of meta-analysis concerning transfusion needs.

5.2. Results

A substantial reduction in 24-h blood loss was confirmed in groups with topical application of tranexamic acid (Fig. 3). The overall weighted mean difference of -321.6 mL (95% CI -530.3, -112.9) significantly differed from zero (p = 0.003). Heterogeneity was found among the trials (I² = 90.8%, p < 0.001).

The proportion of patients requiring red blood cells transfusion was not significantly different (p = 0.887) between the treated and placebo groups (Fig. 4). A variation attributable to heterogeneity was very low.

6. Discussion

This review and the subsequent meta-analysis suggest that topical application of tranexamic acid in cardiac surgery can significantly reduce postoperative bleeding. However, its influence on a statistically significant reduction of transfusion requirements (packed red blood cells) could not be proven, probably due to unduly strict transfusion criteria in the trials (not corresponding with routine everyday practice), a limited number of study patients and a diversity in the concentrations of study solutions.

The anticipated benefit of this way of drug delivery is that the method seems to be both “target-directed” and “potentially safe” [22]. The tranexamic acid blood levels were measured in only one of the above mentioned trials (in a part of topically medicated patients, n = 13) and none of these patients had detectable tranexamic acid levels in their blood samples [17]. The hypothesis that the pericardium acts as a natural barrier that minimizes the rate of systemic absorption is supported by animal experimental studies with different pharmacological agents [25,26]. In the majority of studies the effect on the reduction of blood loss was most pronounced in the first hours after the surgery, which is consistent with a short half-life of tranexamic acid (3 h). Twenty-four hours postoperatively chest tube drainage is
often serosanguinous and theoretically there should be an anti-inflammatory rather than a hemostatic effect of tranexamic acid [27], as fibrinolytic and inflammatory systems are interlinked in the generation of pro-inflammatory cytokines [7].

7. Conclusion

In conclusion, topical use of tranexamic acid is a promising, interesting and effective method for a significant reduction of postoperative blood loss in patients undergoing cardiac surgery, probably without increasing any additional risks to the patients. There is an apparent need for additional randomized, double-blind, controlled trials with large samples of patients focused on the issue of right dosing of topically applied tranexamic acid (volume and concentration), its influence on transfusion requirements and further investigation of the drug safety.

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