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

Tomáš Vaněk, Zbyněk Straka

Kardiochirurgická klinika, Kardiocentrum 3. lékařské fakulty Univerzity Karlovy a Fakultní nemocnice Královské Vinohrady, Praha, Česká republika

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ABSTRACT

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 hours) 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 towards 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.

SOUHRN

Článek se zabývá problematikou topického užití kyseliny tranexamové v kardiochirurgii. V dostupné literatuře byly nalezeny čtyři randomizované, dvojitě zaslepené studie porovnávající kyselinu tranexamovou s placebem (celkem 371 pacientů). Ve všech těchto studiích topická aplikace kyseliny tranexamové signifikantně snížila pooperační krevní ztráty, avšak statisticky významná redukce transfuzních nároků byla popsána pouze v jedné z těchto studií. Metaanalytický přístup potvrdil signifikantní redukci krevních ztrát (za 24 hodin) v průměru o 321,6 ml (95% interval spolehlivosti –530,3 ml, –112,9 ml; $p = 0,003$). Další studie byla provedena s cílem ověřit možnou augmentaci systémového podání kyseliny tranexamové přídavným topickým podáním. Přestože skupina léčená rovněž topickým podáním vykazovala zjevnou tendenci k menším krevním ztrátám, rozdíly mezi skupinami nedosáhly v této studii statistické významnosti. Je zde zřejmá potřeba dalších kontrolovaných studií provedených na větších souborech pacientů.

Adresa: Prof. MUDr. Tomáš Vaněk, CSc., Kardiochirurgická klinika, Kardiocentrum 3. lékařské fakulty Univerzity Karlovy a Fakultní nemocnice Královské Vinohrady, Ruská 87, 100 00 Praha 10, e-mail: vanek@fnkv.cz
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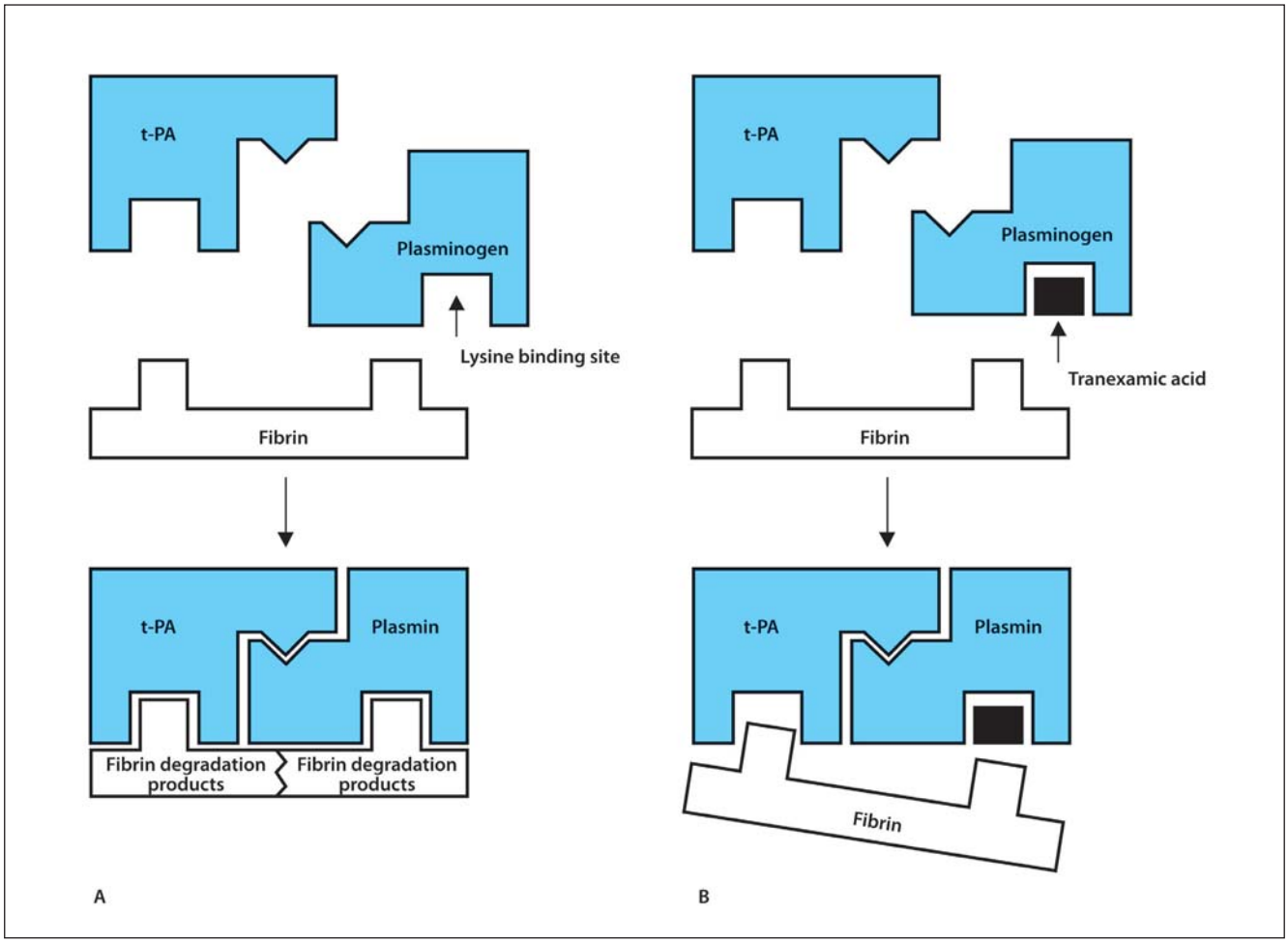

Fig. 1 – Antifibrinolytic action of tranexamic acid. (A) activation of fibrinolysis; (B) inhibition of fibrinolysis.
t-PA – tissue plasminogen activator.
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Introduction

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, ε-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 ε-aminocaproic acid is often applied in the U.S., 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.

Tranexamic acid overview

Tranexamic acid – 4-(aminomethyl)cyclohexane-1-carboxylic acid – is a synthetic derivative of the amino acid lysine. The antifibrinolytic activity is a result of reversible binding to plasminogen which prevents its interaction with fibrin (Fig. 1). Normally, 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,

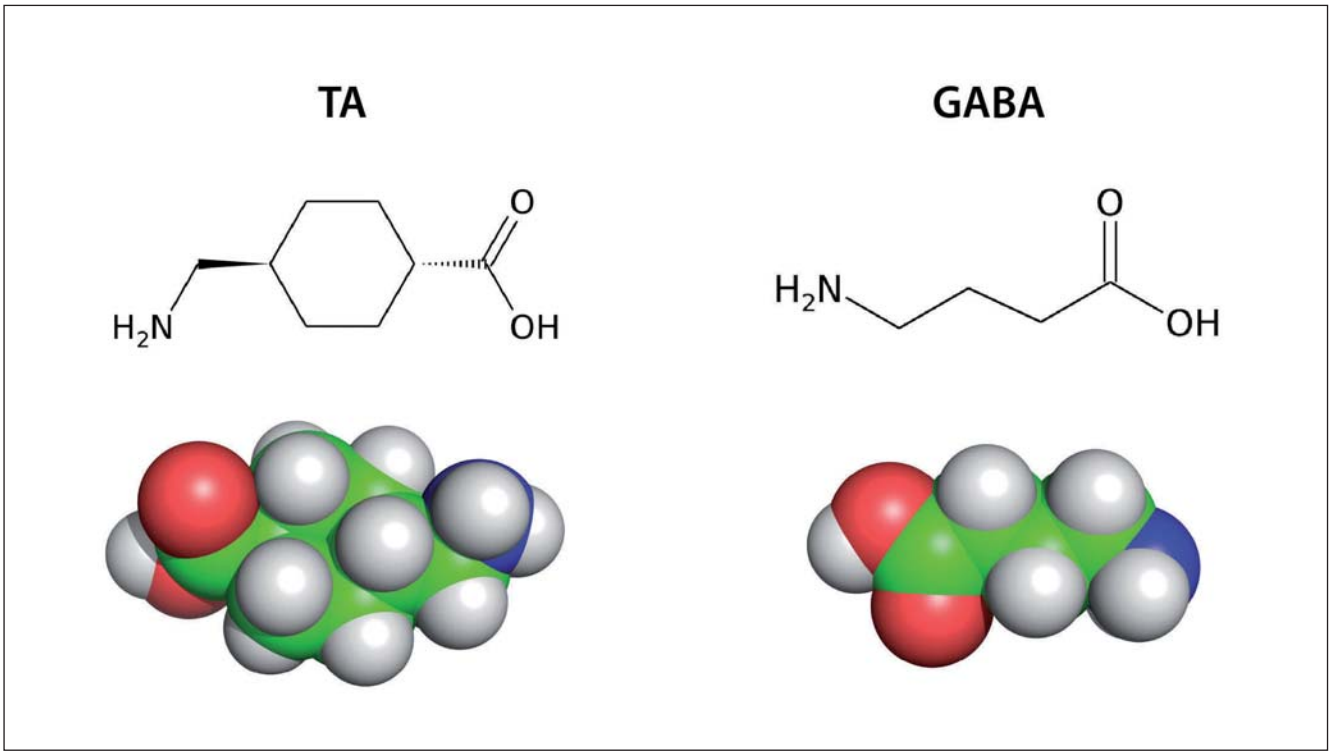

Fig. 2 – Structural formulas and space-filling models of tranexamic acid (TA) and γ-aminobutyric acid (GABA).

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-aminobutyric$_A$ brain receptors [12].

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].

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

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 post-operative transfusion requirements (PRBC)
De Bonis et al. [17]	20	20	1 g TA/100 mL saline	+**	NS
Abul-Azm et al. [18]	50	50	2 g TA/100 mL saline	+****	+***
Baric et al. [19]	97	96	2.5 g TA/250 mL saline	+****[a]	NS[a]
Fawzy et al. [20]	19	19	1 g TA/100 mL saline	+*	NS

PRBC – packed red blood cells; TA – tranexamic acid.
* $p = 0.04$, ** $p = 0.01$, *** $p < 0.01$, **** $p < 0.001$.
[a] Comparison of three groups (aprotinin, n = 100; tranexamic acid, n = 97; placebo, n = 96).

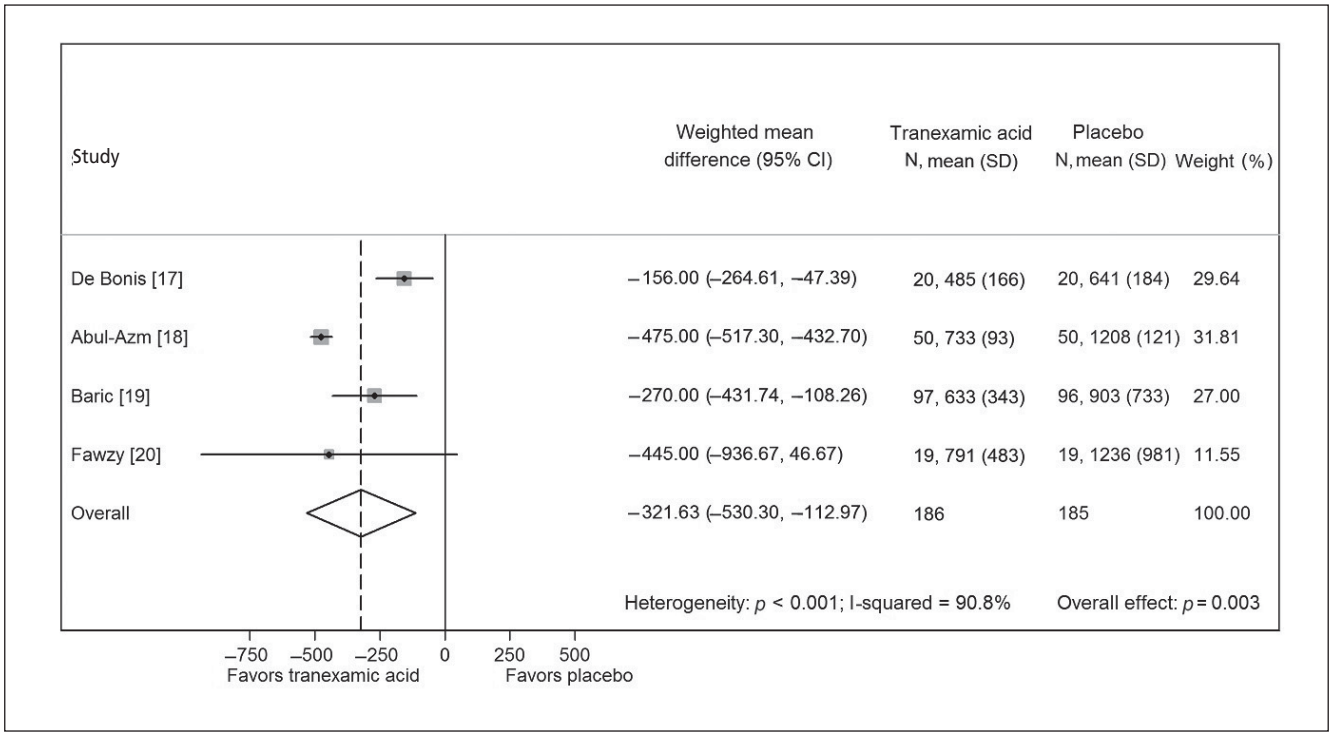

Fig. 3 – Meta-analysis of the studies on topical application of tranexamic acid vs. placebo. Outcomes: the 24-h postoperative chest tube drainage (mL).
CI – confidence interval; SD – standard deviation.

the pericardial 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 hours), but the tendency towards 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 towards lower blood loss in group A was evident (Table 2), no statistical significance was reached at any time points (4, 8, 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, $p = 0.008$).

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

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).

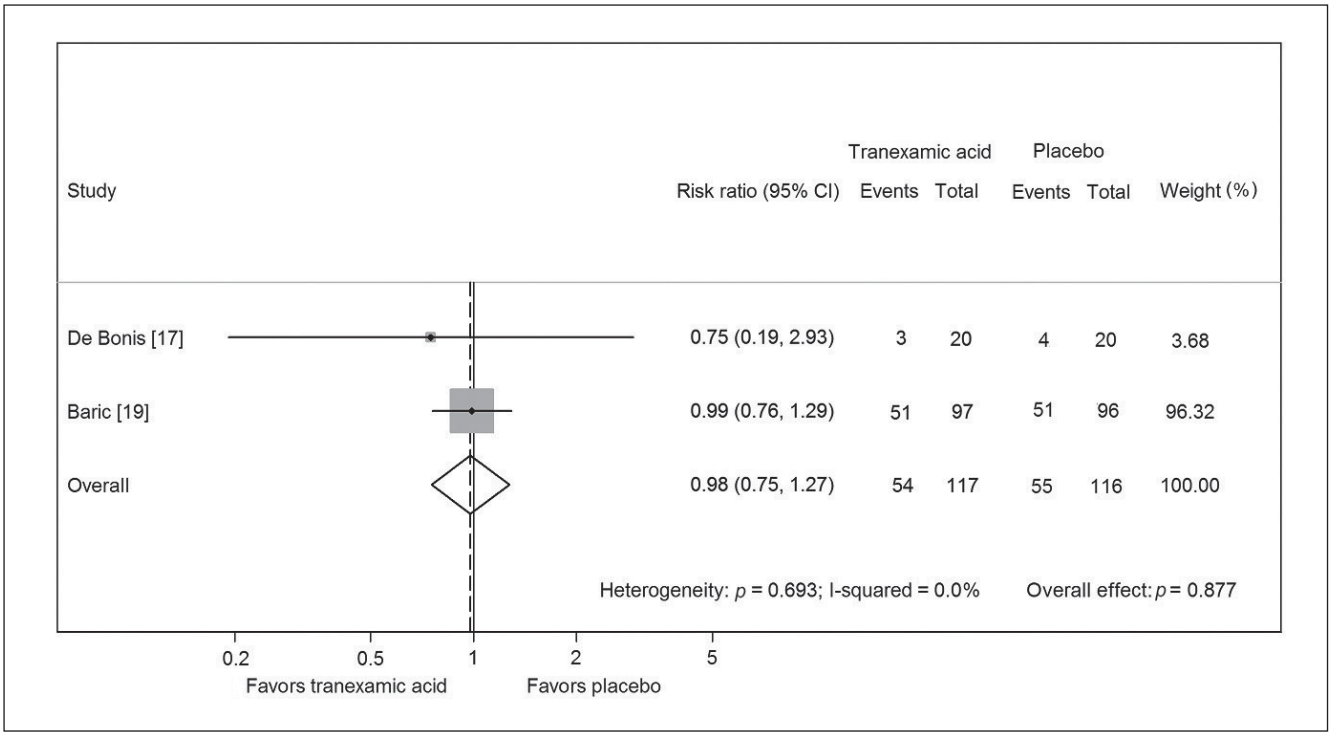

Fig. 4 – Meta-analysis of the studies on topical application of tranexamic acid vs. placebo. Outcomes: the incidence of postoperative transfusion requirements (red blood cells).
CI – confidence interval; SD – standard deviation.

The meta-analysis focused on two primary outcomes: 24 hours 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 I^2 statistics [24]. The chi-squared 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-hour), the calculation was based on the total postoperative chest tube drainage, which did not differ much from that for 24 hours.

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.

Results

A substantial reduction in 24-hour 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 ($I^2 = 90.8\%$, $p < 0.001$).

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.

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

Table 2 – Cumulative blood loss (mL) 4 hours, 8 hours and 24 hours postoperatively (LOST study).

Postoperative time	Group A (n = 49)	Group B (n = 51)	*p*-Value[a]	*p*-Value[b]
4 hours	86.1 (56.1, 132.2)	135.4 (94.3, 194.4)	0.107	0.059
8 hours	199.4 (153.4, 259.2)	261.7 (205.1, 334.0)	0.130	0.050
24 hours	504.2 (436.0, 583.0)	569.7 (476.0, 681.7)	0.293	0.014

Data are presented as geometric means and 95% confidence intervals.
Reproduced from J. Spegar, T. Vanek, J. Snircova, et al., Local and systemic application of tranexamic acid in heart valve surgery: a prospective, randomized, double blind LOST study, Journal of Thrombosis and Thrombolysis 32 (2011) 303–310, with kind permission from Springer Science+Business Media B.V.
[a] Test for equality of geometric means.
[b] Test for equality of variances.

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 hours). 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].

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.

Acknowledgements

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References

[1] K. Karkouti, W.S. Beattie, K.M. Dattilo, et al., A propensity score case-control comparison of aprotinin and tranexamic acid in high-transfusion-risk cardiac surgery, Transfusion 46 (2006) 327–338.
[2] D.T. Mangano, I.C. Tudor, C .Dietzel, The risk associated with aprotinin in cardiac surgery, The New England Journal of Medicine 354 (2006) 353–365.
[3] D.A. Fergusson, P.C. Hébert, C.D. Mazer, et al., A comparison of aprotinin and lysin analogues in high-risk cardiac surgery, The New England Journal of Medicine 358 (2008) 2319–2331.
[4] M. Ranucci, S. Castelvecchio, F. Romitti, et al., Living without aprotinin: the results of a 5-year blood saving program in cardiac surgery, Acta Anaesthesiologica Scandinavica 53 (2009) 573–580.
[5] R.L. Lobato, G.J. Despotis, J.H. Levy, et al., Anticoagulation management during cardiopulmonary bypass: a survey of 54 North American institutions, The Journal of Thoracic and Cardiovascular Surgery 139 (2010) 1665–1666.
[6] C.J. Dunn, K.L. Goa, Tranexamic acid: a review of its use in surgery and other indications, Drugs 57 (1999) 1005–1032.
[7] P.L. McCormack, Tranexamic acid: a review of its use in the treatment of hyperfibrinolysis, Drugs 72 (2012) 585–617.
[8] CRASH-2 trial collaborators, 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, Lancet 376 (2010) 23–32.
[9] J. Ross, S.R. Al-Shahi, The frequency of thrombotic events among adults given antifibrinolytic drugs for spontaneous bleeding: systematic review and meta-analysis of observational studies and randomized trials, Current Drug Safety 7 (2012) 44–54.
[10] K. Martin, G. Wiesner, T. Breuer, et al., The risks of aprotinin and tranexamic acid in cardiac surgery: a one-year follow-up of 1188 consecutive patients, Anesthesia and Analgesia 107 (2008) 1783–1790.
[11] D. Kalavrouziotis, P. Voisine, S. Mohammadi, et al., High-dose tranexamic acid is an independent predictor of early seizure after cardiopulmonary bypass, The Annals of Thoracic Surgery 93 (2012) 148–153.
[12] R. Furtmüller, M.G. Schlag, M. Berger, et al., Tranexamic acid, a widely used antifibrinolytic agent, causes convulsions by γ-aminobutyric $acid_A$ receptor antagonistic effect, The Journal of Pharmacology and Experimental Therapeutics 301 (2002) 168–173.
[13] D.L. Ngaage, J.M. Bland, Lessons from aprotinin: is the routine use and inconsistent dosing of tranexamic acid prudent? Meta-analysis of randomized and large matched observational studies, European Journal of Cardio-thoracic Surgery 37 (2010) 1375–1383.
[14] N. Tabuchi, J. de Haan, P.W. Boonstra, W. van Oeveren, Activation of fibrinolysis in the pericardial cavity during cardiopulmonary bypass, The Journal of Thoracic and Cardiovascular Surgery 106 (1993) 828–833.
[15] P.N. Khalil, M. Ismail, P. Kalmar, et al., Activation of fibrinolysis in the pericardial cavity after cardiopulmonary bypass, Thrombosis an Haemostasis 92 (2004) 568–574.
[16] K.F. Schulz, Assessing allocation concealment and blinding in randomized controlled trials: why bother?, Evidence-Based Medicine 5 (2000) 36–38.
[17] M. De Bonis, F. Cavaliere, F. Alessandrini, et al., Topical use of tranexamic acid in coronary artery bypass operations: a double-blind, prospective, randomized, placebo-controlled study, The Journal of Thoracic and Cardiovascular Surgery 119 (2000) 575–580.
[18] A. Abul-Azm, K.M. Abdullah, Effect of topical tranexamic acid in open heart surgery, European Journal of Anaesthesiology 23 (2006) 380–384.
[19] D. Baric, B. Biocina, D. Unic, et al., Topical use of antifibrinolytic agents reduces postoperative bleeding: a double-blind, prospective, randomized study, European Journal of Cardio-thoracic Surgery 31 (2007) 366–371.

[20] H. Fawzy, E. Elmistekawy, D. Bonneau, et al., Can local application of tranexamic acid reduce post-coronary bypass surgery blood loss? A randomized controlled trial, Journal of Cardiothoracic Surgery 4 (2009) 25.
[21] A. Yasim, R. Aşik, E. Atahan, Effects of topical applications of aprotinin and tranexamic acid on blood loss after open heart surgery (in Turkish), Anadolu Kardiyoloji Dergisi 5 (2005) 36–40.
[22] A. Abrishami, F. Chung, J. Wong, Topical application of antifibrinolytic drugs for on-pump cardiac surgery: a systematic review and meta-analysis, Canadian Journal of Anesthesia 56 (2009) 202–212.
[23] J. Spegar, T. Vanek, J. Snircova, et al., Local and systemic application of tranexamic acid in heart valve surgery: a prospective, randomized, double blind LOST study, Journal of Thrombosis and Thrombolysis 32 (2011) 303–310.
[24] J.P. Higgins, S.G. Thompson, J.J. Deeks, D.G. Altman, Measuring inconsistency in meta-analyses, British Medical Journal 327 (2003) 557–560.
[25] R. Moreno, S. Waxman, K.A. Rowe, R.L. Verrier, Intrapericardial beta-adrenergic blocade with esmolol exerts a potent antitachycardic effect without depressing contractility, Journal of Cardiovascular Pharmacology 36 (2000) 722–727.
[26] T.M. Kolettis, N. Kazakos, C.S. Katsouras, et al., Intrapericardial drug delivery: pharmacologic properties and long-term safety in swine, International Journal of Cardiology 99 (2005) 415–421.
[27] J.J. Jimenez, J.L. Iribarren, L. Lorente, et al., Tranexamic acid attenuates inflammatory response in cardiopulmonary bypass surgery through blockade of fibrinolysis: a case control study followed by a randomized double-blind controlled trial, Critical Care 11 (2007) R117.