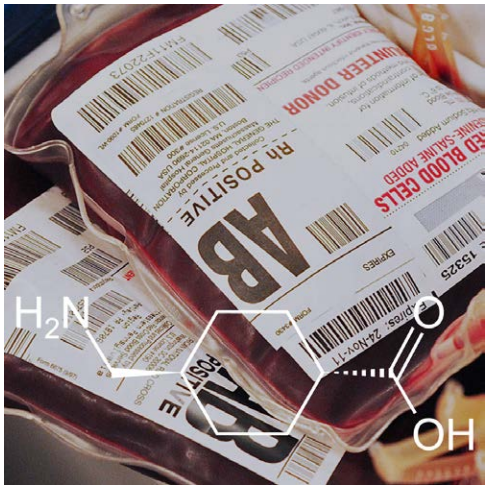
Optimal Tranexamic Acid Dosing Regimen in Cardiac Surgery: What Are the Missing Pieces?

David Faraoni, M.D., Ph.D., F.A.H.A., Jerrold H. Levy, M.D., F.A.H.A., F.C.C.M.

Multiple randomized clinical trials evaluating prophylactic tranexamic acid administration consistently demonstrate a reduction of bleeding and allogeneic blood product transfusion requirements.[1,2] International guidelines recommend prophylactic administration of antifibrinolytic agents in patients undergoing high-risk cardiac surgical procedures.[3,4] In the most recent large trial, patients scheduled to undergo coronary artery bypass surgery and at risk for perioperative complications were randomized to receive either tranexamic acid (50 to 100 mg/kg of actual body weight) or placebo.[5] Tranexamic acid was associated with a lower risk of bleeding than placebo without increase in mortality or thrombotic complications within 30 days of surgery. However, tranexamic acid was also associated with a higher risk of postoperative seizures (0.1% *vs.* 0.7%, $P = 0.002$). In a 1-yr follow-up study, there was no difference in death or severe disability between patients exposed to tranexamic acid or the placebo.[6] Despite the favorable safety profile of tranexamic acid, several questions remain unanswered (fig. 1), and the optimal dose needed to reduce bleeding without increasing the risk of side effects, especially seizures, is still not established.



"…low-dose tranexamic acid (total dose of 20 mg/kg of actual body weight) provides the best balance between reduction in postoperative blood loss and red blood cell transfusion and the risk of clinical seizure."

In this issue of Anesthesiology, Zufferey *et al.* performed a model-based meta-analysis to describe the effect of different tranexamic acid doses on postoperative bleeding and clinical seizures.[7] Their meta-analysis objectives were to estimate the dose-response relationship and identify the optimal dosing regimen to be used in adults undergoing cardiac surgery with cardiopulmonary bypass. The authors included 64 randomized controlled trials and 18 observational studies of intravenous tranexamic acid administration in adult cardiac surgical patients. They found that the plasma concentration required to achieve 50% of maximum effect was 5.6 mg/l (95% credible interval, 0.7 to 11.1 mg/l) or 22.4 mg/l to achieve 80% inhibition of fibrinolytic activation. The authors also reported an increased risk of postoperative clinical seizure incidence of 1.07 (95% credible interval, 1.06 to 1.09) per 10 mg/l increase in tranexamic acid plasma concentration. Compared to no exposure to tranexamic acid, a plasma concentration of 100 mg/l doubled the risk of clinical seizures (2.1; 95% credible interval, 1.9 to 2.4). Among other risk factors, open-chamber procedures and prolonged cardiopulmonary bypass duration both significantly increased the risk of clinical seizures. Using their model-based meta-analysis, the authors conclude that low-dose tranexamic acid (total dose of 20 mg/kg of actual body weight) provides the best balance between reduction in postoperative blood loss and red blood cell transfusion and the risk of clinical seizure. The use of higher doses would only marginally improve the clinical effect at the cost of an increased risk of seizure.

The results reported in this model-based meta-analysis are relevant and an important step toward defining the optimal tranexamic acid dosing regimen in adult cardiac surgical patients. This analysis first integrates the results obtained from large clinical trials with our knowledge of

Image: J. P. Rathmell.

This editorial accompanies the article on p. 165.

Accepted for publication November 6, 2020. Published online first on December 17, 2020. From the Division of Cardiac Anesthesia, Department of Anesthesia and Pain Medicine, The Hospital for Sick Children, Toronto, Canada (D.F.); the Department of Anesthesiology and Pain Medicine, University of Toronto, Toronto, Canada (D.F.): and the Department of Anesthesiology and Critical Care, Duke University School of Medicine, Durham, North Carolina (J.H.L.).

 Anesthesiology 2021; 134:143–6. DOI: 10.1097/ALN.0000000000003637

<zdoi;. DOI: 10.1097/ALN.0000000000003637>

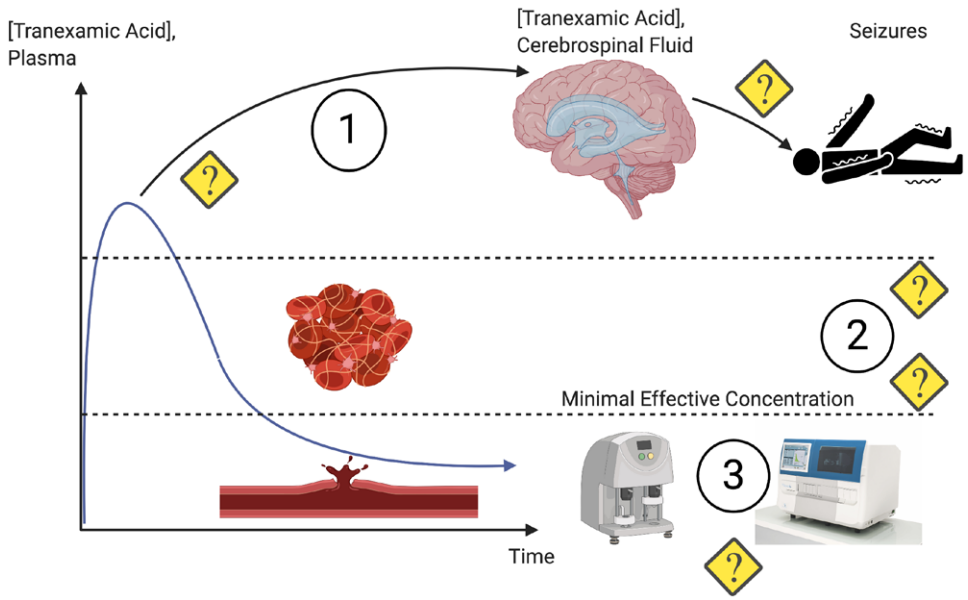


Fig. 1. Infographic summarizing the missing pieces to define the optimal tranexamic acid dosing regimen in cardiac surgery. (1) The true incidence of seizures and the minimal cerebrospinal fluid concentration needed to avoid the risk of seizure and its associated plasma concentration. (2) The range of plasma concentrations required to inhibit fibrinolytic activation. (3) Assays that would better able to estimate the effect of tranexamic acid on fibrinolytic activation *in vivo*. Figure created with BioRender.com.

the tranexamic acid pharmacokinetic profile in adult cardiac surgical patients. By pooling the effects reported in each of the included studies on bleeding, transfusion, and clinical seizures, and by modeling the association between dose regimen and outcomes, the authors were able to confirm that the use of low doses of tranexamic acid (*e.g.*, 20 mg/kg of actual body weight) would suffice to reduce bleeding without increasing the risk of seizures. However, a few important limitations need to be taken into account when interpreting the authors' conclusions for their meta-analysis.

As for any meta-analysis, the quality of the results obtained by pooling data is highly influenced by the quality of the studies included. While all studies included bleeding and transfusion as their primary endpoints, important heterogeneity on the definition of bleeding and transfusion practices can be expected among the studies. Although clinical seizures are an important safety endpoint in trials studying the clinical effect and safety of tranexamic acid, the incidence is relatively low and has been shown to be influenced by preexisting conditions as well as the type of surgical procedure performed. As reported in an experimental model,[8] the peak of tranexamic acid concentration observed in the cerebrospinal fluid was approximately 10% of the peak observed in the plasma and was delayed by 3 to 5 h after peak plasma concentration occured. Due to the complex nature of the relationship between the kinetics of the distribution of tranexamic acid from the plasma to the cerebrospinal fluid and the lack of knowledge about cerebrospinal fluid tranexamic acid concentrations associated with seizures, it is currently impossible to define a dosing regimen that would be predicted to optimize therapeutic plasma tranexamic acid concentrations while maintaining cerebrospinal fluid concentrations below the seizure threshold. In addition, because cardiac surgical patients are sedated when peak concentrations occur in the cerebrospinal fluid, the true incidence of clinical seizures may not be known. Further, current clinical trials were not designed or powered to correlate plasma tranexamic acid levels with the incidence of clinical seizure. The results of the meta-analysis should be interpreted knowing those limitations.

Although the pharmacokinetics of tranexamic acid in adult cardiac surgical patients is known, the dose regimen simulations published based on the pharmacokinetics are targeting plasma concentrations that have never been shown to adequately inhibit fibrinolytic activation *in vivo*.[1] On the basis of the initial investigations from the 1970s, two basic target concentrations have been advocated: a lower concentration of approximately 10 to 20 mg/l, which is thought to inhibit approximately 80% of fibrinolysis, and a high concentration of approximately 100 mg/l, which should completely inhibit fibrinolysis.[9] To date, the minimal effective concentration required to inhibit fibrinolysis was only studied *ex vivo* by addition of high-dose tissue-type plasminogen activator, and the degree of

fibrinolysis was measured with viscoelastic testing, either thromboelastography or thromboelastometry.[10,11] From those studies, the tranexamic acid concentration to effectively inhibit fibrinolysis was in the range of 6 to 15 mg/l. Two important limitations need to be noted. Experiments were performed *ex vivo* in the absence of endothelium and other plasma components that could influence fibrinolytic activation. Further, viscoelastic hemostatic tests have poor sensitivity to detect fibrinolytic activation.[12] Plasmin generation assays have recently been used to measure the impact of intravenous tranexamic acid administration on plasmin generation and fibrinolytic activation. In a cohort of healthy women undergoing cesarean delivery, the ability of the plasmin generation assay to detect the effect of tranexamic acid on fibrinolytic activation was found superior to what could be detected using thromboelastometry.[13] Although such an assay could be seen as a promising tool to estimate the effect of tranexamic acid on fibrinolytic activation in cardiac surgical patients, further *in vivo* clinical studies are needed before the minimal effective concentration of tranexamic acid can be used to define the optimal dosing scheme.

In summary, the model-based meta-analysis published by Zufferey *et al.* in this issue of Anesthesiology confirms the safety and the clinical effect of low-dose tranexamic acid in adult cardiac surgical patients. In order to further refine the optimal dosing scheme, more studies will be needed to complete the missing information required to determine the minimal effective concentration of tranexamic acid to be targeted to inhibit fibrinolytic activation and reduce bleeding, while minimizing the risk of seizures.

Competing Interests

The authors are not supported by, nor maintain any financial interest in, any commercial activity that may be associated with the topic of this article.

Correspondence

Address correspondence to Dr. Faraoni: david.faraoni@sickkids.ca

References

1. Koster A, Faraoni D, Levy JH: Antifibrinolytic therapy for cardiac surgery: An update. Anesthesiology 2015; 123:214–21
2. Levy JH, Koster A, Quinones QJ, Milling TJ, Key NS: Antifibrinolytic therapy and perioperative considerations. Anesthesiology 2018; 128:657–70
3. Task Force on Patient Blood Management for Adult Cardiac Surgery of the European Association for Cardio-Thoracic Surgery (EACTS) and the European Association of Cardiothoracic Anaesthesiology (EACTA), Boer C, Meesters MI, Milojevic M, Benedetto U, Bolliger D, von Heymann C, Jeppsson A, Koster A, Osnabrugge RL, Ranucci M, Ravn HB, Vonk ABA, Wahba A, Pagano D: 2017 EACTS/EACTA guidelines on patient blood management for adult cardiac surgery. J Cardiothorac Vasc Anesth 2018; 32:88–120
4. Raphael J, Mazer CD, Subramani S, Schroeder A, Abdalla M, Ferreira R, Roman PE, Patel N, Welsby I, Greilich PE, Harvey R, Ranucci M, Heller LB, Boer C, Wilkey A, Hill SE, Nuttall GA, Palvadi RR, Patel PA, Wilkey B, Gaitan B, Hill SS, Kwak J, Klick J, Bollen BA, Shore-Lesserson L, Abernathy J, Schwann N, Lau WT: Society of Cardiovascular Anesthesiologists clinical practice improvement advisory for management of perioperative bleeding and hemostasis in cardiac surgery patients. Anesth Analg 2019; 129:1209–21
5. Myles PS, Smith JA, Forbes A, Silbert B, Jayarajah M, Painter T, Cooper DJ, Marasco S, McNeil J, Bussières JS, McGuinness S, Byrne K, Chan MT, Landoni G, Wallace S; ATACAS Investigators of the ANZCA Clinical Trials Network: Tranexamic acid in patients undergoing coronary-artery surgery. N Engl J Med 2017; 376:136–48
6. Myles PS, Smith JA, Kasza J, Silbert B, Jayarajah M, Painter T, Cooper DJ, Marasco S, McNeil J, Bussières JS, McGuinness S, Byrne K, Chan MTV, Landoni G, Wallace S, Forbes A; ATACAS Investigators and the ANZCA Clinical Trials Network: Tranexamic acid in coronary artery surgery: One-year results of the Aspirin and Tranexamic Acid for Coronary Artery Surgery (ATACAS) trial. J Thorac Cardiovasc Surg 2019; 157:644–652.e9
7. Zufferey PJ, Lanoiselée J, Graouch B, Vieille B, Delavenne X, Ollier E: Exposure-response relationship of tranexamic acid in cardiac surgery: A model-based meta-analysis. Anesthesiology 2020; 134:165–78
8. Lecker I, Wang DS, Romaschin AD, Peterson M, Mazer CD, Orser BA: Tranexamic acid concentrations associated with human seizures inhibit glycine receptors. J Clin Invest 2012; 122:4654–66
9. Andersson L, Nilsoon IM, Colleen S, Granstrand B, Melander B: Role of urokinase and tissue activator in sustaining bleeding and the management thereof with EACA and AMCA. Ann N Y Acad Sci 1968; 146:642–58
10. Yee BE, Wissler RN, Zanghi CN, Feng C, Eaton MP: The effective concentration of tranexamic acid for inhibition of fibrinolysis in neonatal plasma *in vitro*. Anesth Analg 2013; 117:767–72
11. Rozen L, Faraoni D, Sanchez Torres C, Willems A, Noubouossie DC, Barglazan D, Van der Linden P, Demulder A: Effective tranexamic acid concentration for 95% inhibition of tissue-type plasminogen activator induced hyperfibrinolysis in children with congenital heart disease: A prospective, controlled, in-vitro study. Eur J Anaesthesiol 2015; 32:844–50

12. Raza I, Davenport R, Rourke C, Platton S, Manson J, Spoors C, Khan S, De'Ath HD, Allard S, Hart DP, Pasi KJ, Hunt BJ, Stanworth S, MacCallum PK, Brohi K: The incidence and magnitude of fibrinolytic activation in trauma patients. J Thromb Haemost 2013; 11:307–14

13. Miszta A, Ahmadzia HK, Luban NLC, Li S, Guo D, Holle LA, Berger JS, James AH, Gobburu JVS, van den Anker J, de Laat B, Wolberg AS: Application of a plasmin generation assay to define pharmacodynamic effects of tranexamic acid in women undergoing cesarean delivery. J Thromb Haemost 2020 [Epub ahead of print]