



The effect of Tranexamic acid on cardiac surgery bleeding

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ABSTRACT

Serious bleeding in cardiac surgery leads to re-exploration, blood transfusion and increases the risks of mortality and morbidity. Using the lysine analogous of antifibrinolytic agents are the preferred strategy to suppress the need for transfusion procedures and blood products. Although tranexamic acid has been very influential in reducing the transfusion requirement after operation, tranexamic acid induced seizures is one of the common side effects of this drug. Due to inhibiting the fibrinolysis, thrombotic events are other possible side effects of using tranexamic acid. There are no certain results regarding decreasing the mortality rate by using the drug but it is identified that tranexamic acid does not increase the mortality. In this article, we aimed to review the literature on using tranexamic acid in cardiac surgeries.

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Introduction

Bleeding and tissue damage may appear as side effects of every surgical operation which immediately activate the homeostatic mechanisms through activation of fibrinolysis and coagulation mechanisms of body to stop losing excessive amount of blood or any thrombosis (1).

Fibrinolytic mechanism inhibits the intravascular deposition of thrombus. The level of the activation of fibrinolytic

mechanism is strongly dependent on the type of surgery which is most significant in orthopedic and cardiac surgeries compared with some simple operations. In each type of surgery, there may be different factors which stimulate the activation of fibrinolysis. Manipulation of the heart, surgical trauma, and heparin are among factors that promote fibrinolysis during cardiac surgeries which finally lead to bleeding and providing the

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situation for blood transfusion procedure (1).

Cardiac operation is among the surgical procedures which rank high in receiving transfused blood products due to bleeding event during or after the operation. In this regard we reviewed the literature on administrating the tranexamic acid during cardiac surgeries.

Blood transfusion

Blood product transfusion is associated with some adverse effects. It is known as a risk factor for higher rate of mortality, infections, and length of hospital stay (2,3).

Safety, cost, and availability of blood products are other noticeable issues which necessitate the investigation of a proper solution to decrease the postoperative blood transfusion requirements. Generally, there are some major risks of recognized or mysterious pathogens along with transfusion including HIV, hepatitis B, and hepatitis C viruses (4).

In previous surveys, a relationship was observed between blood transfusion and poor clinical outcomes. The main strategy to eliminate the need for transfusion and blood product is the administration of antifibrinolytic therapy (5).

Antifibrinolytics

There are several scientific publications which have agreed on beneficial effects of antifibrinolytic agents during hemorrhagic conditions including different types of surgeries, bleeding disorders, hereditary angio-oedema, upper gastrointestinal haemorrhage, menorrhagia, bleeding in pregnancy, etc (6-9).

Antifibrinolytics are haemostatic agents which preserve the blood content and inhibit post or during operation bleeding with different mechanisms of action in the exceptionally complex fibrinolysis

pathway (10). Antifibrinolytics such as tranexamic acid (TXA) and epsilon-aminocaproic acid (EACA), are two synthetically lysine analogue drugs which are used to reduce bleeding caused by various reasons such as several types of surgical procedures in the absence of regulatory mechanisms. Antifibrinolytics function include restraining the fibrinolysis process by blocking the lysine binding sites of plasminogen which results in reducing the interaction of fibrinogen with plasmin and subsequently inhibits the fibrin degradation.

Beneficial effects of antifibrinolytic agents on parameters including platelet count, postoperative bleeding and coagulation are measured in several ways, yielded to a common outcome regarding reduction of the blood product transfusion eventually (11,12).

Tranexamic acid [4-(aminomethyl) cyclohexanecarboxylic acid] is one of the major lysine-like drugs which has shown considerable antifibrinolytic activity in human and firstly described in 1964. TXA has small molecular weight and short half life of about 80 minutes (13).

According to results of the 98 clinical trials performed on urologic orthopedic, gynecologic, hepatic, cranial and orthognathic, cardiac, and oral surgeries, a statistically significant decrease is evident in blood transfusion requirements due to

Table1. Clinical effects of tranexamic acid according to the meta-analysis of Ker et al in 2012 (14)

| Effects of tranexamic acid | Pooled risk ratio |
|-----------------------------------|--------------------------|
| Blood transfusion | 0.62 |
| Myocardial infarction | 0.68 |
| Stroke | 1.14 |
| Deep vein thrombosis | 0.86 |
| Pulmonary embolism | 0.61 |
| Mortality | 0.61 |

administration of tranexamic acid which are summarized in Table 1.

This is a common outcome that does not vary depending on the type of surgery (14). Results obtained through several trials on different types of surgical operations reported that although the effect of tranexamic acid on reducing the mortality events and re-explorations is not statistically significant, it is clear that applying TXA does not increase the mortality rate (14,15).

Higher frequency of re-exploration due to bleeding during or after cardiac surgery has been observed which is noteworthy to be considered (16).

There are numerous investigations concerning the efficacy of prophylactic administration of TXA in patients experiencing cardiac surgeries since the late 1970s. Majority of the trials on cardiac surgeries for example coronary artery bypass graft, valve replacement or repeated surgeries, have tried to compare the value of TXA administration with no drug therapy or applying other drugs including aprotinin, EACA, and desmopresin, in reducing the transfusion procedure. Decrease in allogeneic blood product applying is the major result obtained through various studies.

TXA-induced seizures

All antifibrinolytic drugs have their specific risks and benefits. Although TXA is such a well-tolerated drug, there have been reported some adverse results along with using TXA in patients undergoing cardiac operations including nausea, diarrhea and orthostatic reactions, etc (12). According to some trials, TXA administration can be assumed as a risk factor of seizures after cardiac surgeries which finally lead to higher mortality. The mechanism which results in TXA-induced seizure is uncertain but based on several surveys, this association between

TXA and seizure increases considerably when high dose administration of the drug is used for older patients (17-19). TXA administration has caused seizures with odd ratio of 7.4 (20). The other influential factors on TXA-induced seizures are considered to be the permeability of the blood-brain barrier, inhibiting the GABA neurotransmitter of central nervous system, renal insufficiency of patients, valve surgeries and co-administration of TXA with cephazolin (18,21).

TXA dosin

Although many trials have been performed on the prophylactic administration of TXA for cardiac cases, the optimum dosage of TXA for better effects and maintenance of the drug concentration during the operation are still under discussion. According to studies, nearly 30% of the drug will be cleared by the urine excretion within the 1 hour following administration (22). Although high dose of TXA is observed to be along with higher and steadier plasma concentration of the drug during the surgery, it may increase the risks of different side effects. Therefore some researchers recommended the lowest dosage which is possible to be used as the safest and most appropriate dosage of TXA. A trial in 2010 proposed a bolus of 1gr followed by infusion of 1 gr overnight as a very low dose of TXA which decreases the mortality rate (23). The effective dose of TXA which reduces fibrinolysis activity during in vitro conditions is assessed to be 10 µg/ml.

Majority of data regarding appropriate dose of TXA have been obtained empirically through previous studies which showed a wide range of applied TXA doses. There is not a considerable agreement among researchers regarding the minimum dose of TXA which leads to limiting the bleeding and blood transfusion (11,24). In open heart

surgery, even moderate doses of TXA have resulted in two times increase in the rate of seizure and mortality (25). A trial showed no difference between the efficacy of high and low dosage of administrated TXA on bleeding and transfusion requirements (26). In one survey, about 5.4 mg/kg as the loading dose, 50 mg as the prime dose and 5 mg/kg/h as the amount of infusion were considered as the optimum doses which sustained a steady plasma concentration of above 20 µg/ml. The mentioned doses should be modified in renal deficiency condition (27).

In conclusion, due to the severe risks and high cost associated with blood products and transfusion method, applying TXA has been known as the most comprehensive strategy for decreasing blood transfusion requirements and preserving blood content which has caused considerable health and economic benefits for countries. There is enough evidence to approve the use of antifibrinolytic agents in cardiac surgeries. Different clinical trials have shown the efficacy of TXA on blood transfusion, although the changing rate of mortality and thromboembolysis is yet under debate. Due to low percent of thromboembolic events in trials, obtaining a comprehensive conclusion regarding altered rate of this events by administering TXA is difficult. Despite the better understanding about TXA effect in cardiac surgery, it is still difficult to predict the possibility of occurrence of TXA side effects in individual patients due to various genetics for fibrinolysis and thrombolysis situation.

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Conflict of Interest

The authors declare no conflict of interest.

References

- Daly DJ, Myles PS, Smith JA, et al. Anticoagulation, bleeding and blood transfusion practices in Australasian cardiac surgical practice. *Anaesth Intensive Care*. 2007;35:760-768.
- Rogers MA, Blumberg N, Saint SK, et al. Allogeneic blood transfusions explain increased mortality in women after coronary artery bypass graft surgery. *Am heart J*. 2006;152:1028-1034.
- Murphy GJ, Reeves BC, Rogers CA, et al. Increased mortality, postoperative morbidity, and cost after red blood cell transfusion in patients having cardiac surgery. *Circulation*. 2007;116:2544-2252.
- Hamaguchi I. Blood transfusion and infectious diseases. *Rinsho Byori*. 2013;61:414-417.
- McQuilten ZK, Andrianopoulos N, Wood EM, et al. Transfusion practice varies widely in cardiac surgery: Results from a national registry. *J Thorac Cardiovas Surg* 2013;[Epub ahead of print].
- Tzortzopoulou A, Cepeda MS, Schumann R, et al. Antifibrinolytic agents for reducing blood loss in scoliosis surgery in children. *Cochrane Database Syst Rev*. 2008;3.
- Zufferey P, Merquiol F, Laporte S, et al. Do antifibrinolytics reduce allogeneic blood transfusion in orthopedic surgery? *Anesthesiology*. 2006;105:1034-1046.
- Lethaby A, Farquhar C, Cooke I. Antifibrinolytics for heavy menstrual bleeding. *Cochrane Database Syst Rev*. 2000.
- Chuong CJ, Brenner PF. Management of abnormal uterine bleeding. *Am J Obstet Gynecol*. 1996;175:787-792.
- Schmarts. Antifibrinolytics. *Acta Anaesthesiol Belg*. 2003;54:319-322.
- Dowd NP, Karski J, Cheng D, et al. Pharmacokinetics of tranexamic acid during cardiopulmonary bypass. *Anesthesiology*. 2002;97:309-9.
- Dunn CJ, Goa KL. Tranexamic acid: a review of its use in surgery and other indications. *Drugs*. 1999;57:1005-1032.
- Dhir A. Antifibrinolytics in cardiac surgery. *Ann*

- Card Anaesth. 2013;16:117-125.
14. Ker K, Edwards P, Perel P, et al. Effect of tranexamic acid on surgical bleeding: systematic review and cumulative meta-analysis. *BMJ*. 2012;344:e3054.
 15. Henry D, Carless P, Moxey A, et al. Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion (Review). *Cochrane Database Syst Rev*. 2011.
 16. Guenther CR. Pro: tranexamic acid is better than aprotinin in decreasing bleeding after cardiac surgery. *J Cardiothorac Vasc Anesth*. 1994;8:471-473.
 17. Bell D, Marasco S, Almeida A, et al. Tranexamic Acid in cardiac surgery and postoperative seizures: a case report series. *Heart Surg Forum*. 2010;13:E257-259.
 18. Murkin JM, Falter F, Granton J, et al. High-dose tranexamic acid is associated with nonischemic clinical seizures in cardiac surgical patients. *Anesthesia and analgesia*. 2010;110:350-353.
 19. Montes FR, Pardo Df, Carreno M, et al. Risk factors associated with postoperative seizures in patients undergoing cardiac surgery who received tranexamic acid: a case-control study. *Ann Card Anaesth*. 2012;15:6-12.
 20. Manji RA, Grocott HP, Leake J, et al. Seizures following cardiac surgery: the impact of tranexamic acid and other risk factors. *Can J Anaesth*. 2012;59:6-13.
 21. Martin K, Wiesner G, Breuer T, et al. The risks of aprotinin and tranexamic acid in cardiac surgery: a one-year follow-up of 1188 consecutive patients. *Anesth Analg*. 2008;107:1783-1790.
 22. Lecker I, Wang DS, Romaschin AD, et al. Tranexamic acid concentrations associated with human seizures inhibit glycine receptors. *J Clin Invest*. 2012;122:4654-4666.
 23. Shakur H, Roberts I, Bautista R, et al. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. *Lancet*. 2010;376:23-32.
 24. Verstraete M. Clinical application of inhibitors of fibrinolysis. *Drugs*. 1985;29:236-261.
 25. Koster A, Borgermann J, Zittermann A, et al. Moderate dosage of tranexamic acid during cardiac surgery with cardiopulmonary bypass and convulsive seizures: incidence and clinical outcome. *Br J Anaesth*. 2013;110:34-40.
 26. Armellin G, Vinciguerra A, Bonato R, et al. Tranexamic acid in primary CABG surgery: high vs low dose. *Minerva Anesthesiol*. 2004;70:97-107.
 27. Fiechtner BK, Nuttall GA, Johnson ME, et al. Plasma tranexamic acid concentrations during cardiopulmonary bypass. *Anesth Analg*. 2001;92:1131-1136.