Systematic Review of Major Outcomes of Tranexamic Acid in Cardiac Surgery

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Abstract

Introduction: In the context of heart surgery, minimizing blood loss during surgery is critical. Tranexamic acid (TA) is an antifibrinolytic agent that has been widely used in other surgical specialties, especially in cardiac. Severe bleeding after cardiac surgery occurs in 3.0 to 11.0% of cases and requires surgical re-exploration in around 5.0% of cases.

Objective: Conducted a systematic review in order to present the main literary findings on the use of tranexamic acid in the context of cardiac surgery.

Methods: Following literary search criteria with the use of the MeSH Terms that were cited in the item on "Search strategies", a total of 84 clinical studies that were submitted to the eligibility analysis were checked and after that, 22 studies were selected, following the rules of systematic review-PRISMA.

Major findings: The findings of this meta-analysis suggest that intrapericardial use of TA in patients undergoing cardiac surgery may decrease bleeding postoperatively without increasing the risk of postoperative seizures. The target concentration of TA to effectively inhibit fibrinolysis during CPB is 10-20 µg/L. The most frequent adverse effects reported with the use of TA are minor gastrointestinal symptoms, such as nausea and vomiting, especially when given in high doses or injected rapidly.

Conclusion: With the use of tranexamic acid, some issues such as the incidence of thrombotic complications still require better elucidation, as well as the route of topical administration. Some authors have recommended a beginning infusion of such drugs after full heparinization in myocardial revascularization surgery, arguing that such a practice does not alter the outcome in terms of bleeding and would reduce the incidence of thrombotic complications.

Introduction

In the context of heart surgery, minimizing blood loss during surgery is critical. The use of pharmacological agents, such as antifibrinolytics, has been shown to significantly reduce blood loss and postoperative blood transfusion rates in many articles [1]. Thus, tranexamic acid (TA) is an antifibrinolytic agent that has been widely used in other surgical specialties, especially in cardiac, orthopedic and traumatological surgeries. Despite its known benefits, the use of TA in plastic surgery is extremely limited, mainly because most plastic surgery procedures do not involve the extent of blood loss that can lead to anemia and the need for blood transfusion [1].

Most of the time, cardiac surgery is accompanied by perioperative bleeding and complications associated with blood transfusion and components [2]. Bleeding can occur either due to inadequate surgical hemostasis or abnormality in coagulation as a consequence of extracorporeal circulation (ECC) [2]. Thus, the cause of bleeding in cardiac surgery is multifactorial and related to surgical complexity, heparin use, multiple hemostatic changes of CPB, vascular damage during surgery, hypothermia, fibrinolysis, hemodilution, microvascular damage and hemostasis quality [2-6]. As epidemiological data, severe bleeding after cardiac surgery occurs in 3.0 to 11.0% of cases and requires surgical re-exploration in around 5.0% of cases. Of these, 50.0 to 60.0% are identified as inadequate surgical hemostasis and are associated with a 3- to 4-fold increase in mortality [7].

Also in this context, severe bleeding after cardiac surgery has been attributed to changes in the coagulation system as a result of surgical trauma and the use of CPB [7]. It activates a variety of hemostatic processes, including coagulation and fibrinolysis, leading to increased risk of bleeding and postoperative thrombosis [7]. Surgical trauma and bleeding stimulate extrinsic and intrinsic mechanisms, initiating the coagulation cascade [8].

Tissue and plasma thromboplastins cause prothrombinase to become a prothrombin activator, allowing thrombin to stimulate fibrinogen to form a fibrin network to stop bleeding [8]. Furthermore, plasminogen and plasmin are activated by lysine and degrade the fibrin network so that the blood returns to circulation [9].

Therefore, as a prophylactic and curative measure, TA is part of the antifibrinolytic derivatives derived from the amino acid lysine [10]. Among other antifibrinolytics, TA has an affinity for plasminogen; its antifibrinolytic activity is more sustained and has a longer action time. It has a distribution volume of 9 to 12 liters and elimination half-life around two hours [10]. After venous injection, only 3.0% binds to proteins. However, more than 95% of the drug is eliminated by urine, therefore, in patients with renal impairment; the dose should be reduced [10]. TA inhibits fibrinolysis by competition with the lysine molecule at the fibrinogen and plasmin coupling sites after the coagulation cascade, and thus decreases the degradation rate of the fibrin network reducing bleeding [7,8].

Therefore, the present study has conducted a systematic review in order to present the main literary findings on the use of tranexamic acid in the context of cardiac surgery.

Methods

Study design

Following literary search criteria with the use of the MeSH Terms that were cited in the item on "Search strategies", a total of 84 clinical studies that were submitted to the eligibility analysis were checked, and after that, 22 studies were selected, following the rules of systematic review-PRISMA (Transparent reporting of systematic reviews and meta-analyzes-http://www.prisma-statement.org/).

Search strategy and information sources

The search strategy was performed in PubMed, Embase, Ovid and Cochrane Library, Web of Science, ScienceDirect Journals (Elsevier), Scopus (Elsevier), OneFile (Gale) followed the following steps: search for MeSH Terms: Cardiac surgery; Tranexamic acid; Tranexamic acid treatment; Blood coagulation; Meta-analysis; Systematic review; Clinical trial - use of boolean "and" between mesh terms and "or" among historical findings.

Risk of bias

According to the Cochrane model for risk of bias in the present study, the overall assessment resulted in 4 studies with high bias risk and 2 studies with uncertain risk. In addition, there was an absence of funding source in 3 studies and four studies did not disclose the information on the declaration of conflict of interest.

Literature Review

In cardiac surgery, fibrinolysis can occur through a skin incision, sternotomy, pericardiotomy, and extracorporeal circulation [1]. Most efficacy assessments of antifibrinolytic agents use an infusion of such drugs initiated prior to skin incision, i.e., pre-heparinization [2-5]. TA is a lysine analog that inhibits fibrinolysis by competitively blocking high-affinity lysine binding sites in plasminogen, thereby preventing the formation of the complex between plasminogen, fibrin and tissue plasminogen activator [6,7]. It presents the low molecular weight, hydrophilicity, renal elimination largely unchanged and low cost, besides having a plasma half-life time very close, around two hours [7].

TA is six to 10 times more potent than other antifibrinolytics [7]. TA significantly decreases postoperative blood loss, with marked variation (50-460 mL) [7]. Total perioperative blood loss reduces, on average, 440 mL [7]. In most studies, the reduction of re-operations by bleeding did not present statistical significance. TA is rapidly eliminated in patients undergoing heart surgery with CPB when given in a single dose [8,9].

A meta-analysis study was conducted to investigate the efficacy and safety of AT in cardiac surgery. A total of seven randomized controlled trials (six with and without extracorporeal circulation) comparing the topical application of TA to placebo in 692 patients were eligible for blood loss outcome data. These studies randomized 372 patients to receive AT and 320 patients as controls. The use of intrapericardial TA was associated with a considerable reduction in 24-hour blood loss in all seven studies and a weighted mean difference of -343.56 mL (95% confidence interval: -316.41, -370, 72) (p=0.005) with heterogeneity of I 2=0%. Therefore, the findings of this meta-analysis suggest that intrapericardial use of TA in patients undergoing cardiac surgery may decrease bleeding postoperatively without increasing the risk of postoperative seizures [3,11-15].

The optimal dose schedules for AT are based on empirical dose-response studies and pharmacokinetic models [10]. Other authors recommend a dose of 10 mg/kg for 30 minutes after anesthetic induction and before skin incision, followed by continuous infusion of 1 mg/kg/h for 12 hours [10]. These authors concluded that this scheme was sufficient to reduce bleeding after CPB and those high doses did not provide additional hemostatic benefits. The authors Dowd et al. [16] suggested a dose of 12.5 mg/kg followed by a continuous infusion of 6.5 mg/kg/h associated with 1 mg/kg of the drug dissolved in the solution of the CPB circuit [15]. The target concentration of TA to effectively inhibit fibrinolysis during CPB is 10-20 µg/L [15].

In this context, there is concern about the prothrombotic effects of this drug and the increased risk of vascular events [16]. In cardiac surgery with CPB, TA infusion after heparinization and through a peripheral venous catheter has been recommended [16]. However, systematic reviews and meta-analysis do not confirm these concerns [16-20]. The most frequent adverse effects reported with the use of TA are minor gastrointestinal symptoms, such as nausea and vomiting, especially when given in high doses or injected rapidly [17-19].

A randomized, double-blind study compared the efficacy of epsilon aminocaproic acid (EACA) to AT in reducing blood loss

and transfusion requirements in patients undergoing cardiopulmonary bypass surgery. The findings of this study suggest that EACA and AT have similar effects on thoracic drainage, but EACA is associated with fewer transfusions in isolated myocardial revascularization surgeries [2].

Moreover, the evaluation made by Martin et al. [21] in patients undergoing cardiac surgery with CPB showed increased seizures associated with the use of TA when compared with other antifibroliticos. In addition, persistent atrial fibrillation was also associated with the use of AT, according to Martin et al. [21]. However, these complications may be associated with the prolonged use of high doses of this medication.

Other benefits of using TA are that blood exposed to foreign surfaces of the CPB circuit, endotoxemia, and ischemia-reperfusion injury have contributed to the inflammatory response associated with cardiac surgeries. Factors associated with this response are complement activation, coagulation, and fibrinolytic system activation. Interleukin 6 and 8 (IL-6 and IL-8) are two proinflammatory cytokines that are known to increase during and after cardiac surgery with CPB. Elevated levels of these cytokines after CPB are associated with increased risk of organ damage and death [22].

Greilich et al. [22] followed 60 patients comparing serum levels of D-dimer (fibrinolysis marker), IL-6 and IL-8 before, during and after cardiac surgery with CPB. Similarly this study demonstrated that BP significantly reduced levels of D-dimer and IL-8 in patients undergoing cardiac surgery with CPB. The results indicate that the effects of TA on IL-6 and IL-8 (proinflammatory cytokines) are due to inhibition of either excessive plasmin activation or D-dimer formation or to both [22].

Another proposal found in the present study was the topical use of TA [15]. Due to the theoretical risks related to the systemic use of antifibrinolytics and recognition of the natural barrier properties of the pericardium, preventing substance-free diffusion, studies have been published evaluating the efficacy of these agents when used topically [15]. In addition to reduced systemic absorption, potentially with less adverse effects, another reason for the topical administration of antifibrinolytic would be the direct action on the focus of increased fibrinolytic activity [15].

It is known that under physiological conditions human pericardium contains large amounts of tissue plasminogen activator, which ensures fluidity of the pericardial fluid and prevents the formation of adhesions [15]. Therefore, some authors have demonstrated that, in patients undergoing cardiac surgery, the antithrombin/thrombin complex levels and fibrin degradation products are significantly increased in the pericardial cavity fluid in relation to the systemic levels, demonstrating the magnitude of the local fibrinolytic activity [15].

A review was published in which studies comparing topical administration of TA and placebo was evaluated [15]. The results favored the use of the antifibrinolytic agent. Ker et al. [20] published a meta-analysis analyzing the use of topical TA to assess bleeding as well as the incidence of DVT and concluded that there is evidence that topical use of TA decreases bleeding but effects on the risk of thromboembolism are still uncertain.

A current observational study showed that among 341 Canadian academic cardiac anesthetists, 234 completed the survey (response rate 68.2%). Among the interviewees, 86.3% administer TA to all patients; 13.7% administer it in some. The mean (standard deviation) dose administered was 49 mg/kg (24), with a range of 10 to 100 mg/kg. The mean dose varied between the provinces from 23 to 55 mg/kg. Further research is needed to determine the dose of AT that maximizes efficacy and minimizes side effects [4].

Another retrospective study evaluated the incidence of non-ischemic postoperative seizures associated with the use of AT and the possibility of prevention with a low dose regimen of TXA. A total of 12,195 patients who underwent cardiac surgical procedures under extracorporeal circulation were evaluated. Low-dose AT was associated with fewer seizures than high-dose TXA (46 of 7,452 cases (0.70%) versus 34 of 2,190 cases (1.55%), respectively, $p < 0.0001$). CPB was also associated with a higher incidence of seizures compared to revascularization (80 of 6.662 (1.20%) and 11 of 5.533 (0.20%), respectively, $p < 0.0001$) [5].

Sharma et al. [6] examined the effect of TA on coagulation at different times during cardiac surgery using rotational thromboelastometry. Sixteen adult men were recruited for cardiopulmonary bypass (CPB) surgery for the first time. Ten patients received anesthesia and nine did not receive anesthesia. The times of analysis of rotational thrombocytometry occurred before anesthesia, after sternotomy, after heparinization and CPB surgery, and after administration of protamine (sternal closure). Patients with AT had two prolonged coagulation times (all tests), indicating reduced thrombin generation and lower clot fibrinogen. After CPB, coagulation times in both groups were prolonged. After protamine sternum closure, coagulation time remained prolonged in both groups. Patients with TXA also had a 37.0% reduction in platelet count [6].

Discussion

In a retrospective study, it was investigated whether the use of TA could increase postoperative stroke in cardiac surgery. 2,016 patients underwent cardiac surgery, 664 patients received intravenous TA infusion and 1,352 patients did not receive. Intraoperative TA administration was associated with postoperative stroke (1.7% vs. 0.5%, and coma in cardiac surgery.) [7] As subtype analysis was performed, TA administration was still associated with postoperative vascular accident (1.7% vs. 0.3%) in patients submitted to valve surgery or multi-valve surgery, but was not associated with postoperative stroke in patients submitted to myocardial revascularization surgery alone. However, TA administration was not associated with postoperative mortality, seizure, continuous renal replacement therapy, and re-sternotomy for postoperative bleeding. There was no difference in postoperative ventilation time, duration of intensive care unit and duration of hospitalization [7].

The authors Myles et al. [8] found that the risk of death was not significantly higher with TA than with placebo among patients undergoing cardiac surgery. Doses that are less than 50.0 mg per kilogram body weight are effective in preventing bleeding as well as in reducing the inflammatory response associated with extracorporeal circulation. Another important finding was that patients with the 5G/G genotype had a greater blood-sparing benefit with the use of AT than those with the type-1 plasminogen inhibitor type 4G genotype [6]. It will be important that future studies take into account the pharmacogenomics of TA to adequately adjust the dosage and to reduce the risk of dose-related adverse effects.

In addition, the TA test for coronary surgery showed was associated with less bleeding than placebo, with no increased risk of thrombotic complications or death [11]. However, BP was associated with an incidence of postoperative seizures that was 7 times greater than the incidence with placebo, and patients with seizures were more likely to have a stroke or die within 30 days after surgery [11].

The cause is that TA is a competitive antagonist of glycine and γ-aminobutyric acid type A (GABAA) receptors and causes a concentration-dependent reduction in inhibitory neurotransmission. Commonly used general anesthetics, including propofol and sevoflurane, which increase the function of the glycine receptor and the GABA A receptor, rapidly reverse the inhibition of AT of these receptors.1 Thus, the likelihood of seizures can be reduced by reducing the dose of TA and the administration of anesthesia during the early postoperative period, particularly in patients who are at risk of elevated AT levels during surgery [11].

Conclusion

With the use of tranexamic acid, some issues such as the incidence of thrombotic complications still require better elucidation, as well as the route of topical administration. Some authors have recommended a beginning infusion of such drugs after full heparinization in myocardial revascularization surgery, arguing that such a practice does not alter the outcome in terms of bleeding and would reduce the incidence of thrombotic complications.

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