Review

Tranexamic Acid Use In Cardiac Surgery: A Review On Indications, Dosage, And Complications

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Abstract

It has been demonstrated that cardiovascular diseases are one of the most common causes of death in humans; therefore, various prevention and treatment measures are being taken by the medical community in this regard. For a long time, various treatments have been recommended, including surgeries, but these methods may have a number of complications that the most important of which is bleeding after surgery. Therefore, preserving a patient's blood during heart surgery is very important. Due to the high number of patients undergoing heart surgery and the high probability of using blood products, regardless of the costs to be paid, there is a wide range of known and unknown and at the same time unwanted complications and conditions that can be caused by blood transfusions. Therefore, researchers have conducted several studies to find ways to preserve the blood of patients undergoing heart surgery, including the use of drugs such as tranexamic acid (TXA). TXA is a synthetic analog of the amino acid lysine and an anti-fibrinolytic compound that competitively inhibits plasminogen-to-plasmin activation. This compound non-competitively blocks plasmin at high concentrations, thus TXA prevents the dissolution and destruction of fibrin clots by plasmin. An extensive review of literature has shown that TXA has prevented bleeding in multiple trials without increasing the risk of thrombosis and has a wide range of clinical uses. Despite the role of tranexamic acid in reducing postoperative bleeding, however, the use of this drug will have several side effects. Due to the contradictory results of different literature related to the use of this drug in reducing bleeding and also reducing the need for blood transfusion in patients undergoing surgery, the present review study was conducted to investigate the literature on this subject.

Keywords: Tranexamic acid, cardiac surgery, antifibrinolytic agents, blood conservation.

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Introduction

Cardiovascular diseases are the most common cause of death in patients which endanger the life of thousands of patients every year [1]. It is estimated that one in three adults in the United States has one or more cardiovascular diseases [2]. According to statistics released by the World Health Organization and the Center for Disease Control and Prevention in 2008, about 17.3 million people died worldwide from these diseases, which it is accounts for a 30 percentage of all deaths, and half of them have coronary artery disease [3]. Global statistics show that about 52% of deaths in the United States and 48% in Europe are due to these diseases [4]. It is also predicted that by 2030, about 23.6 million people will die from cardiovascular disease [5]. These diseases cause many problems for patients and high costs for society. Due to the importance of the subject, various methods are used in the treatment of cardiovascular diseases, one of which is surgery, which leads to a reduction in mortality from this disease [6]. About 60% of patients suffering from coronary artery disease undergo surgery [7].

Most patients who undergo heart surgery are uncomplicated in the hospital, but heart surgery has many risks [8]. This surgical method, like all surgical methods, has a number of complications, the most important of which is bleeding after surgery [9]. Due to the high number of patients undergoing heart surgery and the high probability of using blood products, regardless of the costs to be paid, there is a wide range of complications and conditions related to blood transfusion. Therefore, researchers have conducted several studies in order to find ways to preserve the blood of patients undergoing heart surgery, including the use of drugs such as aminocaproic acid, aprotinin and tranexamic acid [10-12]. There is disagreement in the literature on the use of Tranexamic Acid (T.A.) to prevent bleeding. Some researchers believe in using this drug to reduce bleeding and reduce the need for blood transfusions, and some suggest other drugs.

Search strategy

We conducted a review study using Google Scholar, MEDLINE / PubMed and Scopus databases to search for relevant trials, till April, 2021. The search was performed using different combination of keywords including Tranexamic acid, cardiac surgery, antifibrinolytic agents, fibrin modulating agents, hemorrhage, bleeding, and blood conservation. No language or template restrictions were used on the search. Additionally, the bibliography of retrieved papers was also examined to identify other relevant publications. A total of 189 studies were identified, which of them 65 studies were considered and summarized related to this study. Issues related to Tranexamic acid use in cardiac surgery including mechanisms of action, indications, dosage, administration and complications investigated in this study. We

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first review the mechanisms of action and then the usage and efficacy, dosage, risk factors, indications and adverse effects associated with this antifibrinolytic agent.

Cardiac surgery: bleeding and blood transfusion

Bleeding in patients can be the result of a variety of factors, including surgery, trauma, complications of obstetrics and gynecology, and impaired blood clotting. Meanwhile, bleeding in cardiovascular surgery is a major complication that prolongs hospital stay, increases the need for blood transfusions, and leads to overall mortality from complications such as thrombotic events and stroke [13]. The first complication in cardiac surgery is hemorrhage and is actually 15-20% of the use of blood products in the United States in cardiac surgery [14]. In general, blood loss and subsequent transfusions are associated with major complications and mortality [15, 16]. Coronary artery bypass grafting (CABG) surgery requires different amounts of blood [17]. Up to 90 million units of red blood cells are injected annually worldwide [18]. According to the Adult Cardiac Surgery Database (ACSD), 92.8% of blood use is allocated to coronary surgery [19]. Also, the rate of blood transfusion in a study in 13 CABG centers in 2020 has been reported from 10.9 to 59.9% [20].

It seems that the main cause of bleeding is impaired platelet function and coagulation factors due to contact of the patient's blood with the cardio-pulmonary pump (CPP) [21, 22]. Abnormal bleeding in CABG surgery has been reported to be 2-5% [23]. Also in studies, about 3% of patients need to reoperation due to heavy bleeding [24]. Finally, preserving patient's blood during heart surgery is very important. Because increased bleeding from surgery is associated with an increased risk of cardiac tamponade, the need for blood transfusions, reoperation of the heart, increased hospital and patient costs, and ultimately increased morbidity and mortality. Therefore, due to the variety of causes of bleeding, it is necessary to use anti-fibrinolytic drugs, which are often used for this purpose.

Over the years, the use of drugs to reduce bleeding in cardiac surgery patients has become very popular. The use of anti-fibrinolytic drugs can reduce blood loss in heart surgery and non-surgical diseases. Evidence of their effectiveness has been increasing for years [25, 26]. One of these drugs is tranexamic acid for use in patients undergoing heart surgery [11]. Some studies have reported that tranexamic acid significantly reduces blood loss, thereby reducing the need for blood transfusions [27-29]. On the other hand, some studies have concluded that the administration of tranexamic acid has no effect on postoperative bleeding [30, 31]. In one study, preoperative use of TXA in patients at risk for bleeding under coronary artery bypass grafting was associated with a reduction in bleeding

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without a detectable increase in thrombotic complications within 30 days after surgery compared with placebo [32]. The results of the above study showed that postoperative thrombotic events, blood transfusion needs and reoperation due to major bleeding or cardiac tamponade were significantly reduced in the TXA group. However, postoperative seizures were higher in those who received TXA (0.7% vs. 0.1%, initial trial dose was 50 mg / kg IV). Recently, the results of an extensive meta-analysis by Yao et al. [33] showed that TXA injection significantly reduced postoperative bleeding volume in adult and pediatric patients and in a variety of surgical procedures. The results of this study also showed that TXA significantly reduced the volume of red blood cell (RBC) transfusion [33].

Tranexamic acid: mechanism of action

Synthetic antifibrinolytics such as tranexamic acid (TXA, trans-4- aminomethylcyclohexane-1-carboxylic acid) and Epsilon Aminocaproic Acid (ε ACA) are analogue of lysine [1]. These agents, first described by S. Okamoto in 1957, bind to plasminogen and plasmin and inhibit fibrinolysis by blocking lysine binding sites on plasminogen molecules [34]. Thus, inhibition of plasminogen activation leads to stabilization of the fibrin network already made by secondary homeostasis (this improves clot formation, stability, and duration) [13]. Tranexamic acid is available in intravenous and oral formulations. Oral and intravenous TXA bioavailability has been reported to be 33 – 34% [35]. Tranexamic acid is six to 10 times stronger and has a longer half-life than ε- ACA [36]. For intravenous TXA, a half-life of about 2 hours has been reported in healthy volunteers [13]. Removal of the intravenous form of TXA is approximately 90% over a 24-hour period, which is the major excretion mechanism through renal clearance [37, 38]. TXA has been shown to increase thrombosis formation in a dose-dependent manner in animal models [39]. Evidence from several studies suggests that TXA inhibits plasmin-induced platelet activation in extracorporeal flow, such as cardiopulmonary bypass (CPB) used in cardiac surgery [40].

There are several factors that lead to bleeding following CPB, and fibrinolysis is one of the few that can be reduced with medication. TXA also reduces excessive bleeding after CPB by several other mechanisms [41]. 1) The interaction of plasmin and platelets leads to the selective release of ADP granules from platelets, which is caused by contact of the platelet surface with the extracorporeal circulation [42]. 2) TXA may reduce the inflammatory response and associated hemodynamic instability in patients with CPB [43]. 3) Hyperfibrinolysis helps to coagulation disorders in trauma [44]. 4) There are beneficial interactions of TXA with desmopressin, which significantly reduces the blood loss and blood transfusion [45].

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Table 1. Review on Selected articles on Tranexamic acid

First Author/ year	Indications	Study/Dose/Administration time	Important findings	Ref.
Yao/2020	cardiac surgery	Systematic review and meta-analysis	TXA significantly reduced post-operative blood loss and transfusion requirement	33
Besser/2020	Cardiac Surgery	D-dimer levels: 0.5-5.0 mg/L	A decrease or increase in D-dimer levels during surgery was influenced significantly by a higher or lower tranexamic acid dose	73
Cai/2019	Clinical	Overview	TXA is a non-specific hemostatic agent with numerous clinical uses.	13
Beverly/2019	cardiac surgery	Systematic review and network metaanalysis	TXA improves clot formation, stability, and duration.	74
Gerstein/2018	CardiacSurgery	-	TXA's use in cardiac surgery reduces bleeding risk without a Concomitant increase in thromboembolic complications or an increase in mortality.	72
Myles/2017	coronary artery surgery	100 mg/kg IV (later 50 mg/kg) of body weight administered >30 min after the induction of anesthesia	Moderate—Largely doubleblinded study with good outcomes with perioperative care	32
Yang/2017	Valve replacement surgery	10-15 mg/kg iv	Reduced postoperative bleeding and blood transfusion.	75
Negargar/2016	coronary artery bypass graft surgery	pre and post-pump tranexamic acid	Pre-pump administration of TA had a similar result with post-pump TA administration in terms of bleeding during surgery and need for transfusion	71
Ng /2015	Clinical	Review	TXA is an antifibrinolytic treatment applied in a perioperative setting	41

In general, TXA suppresses fibrinolysis, which is manifested by a decrease in serum D-dimer levels but does not affect the results of serum blood coagulation markers. In addition, co-administration of heparin does not affect

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TXA activity and makes it a useful drug in heparinized patients [46].

Various indications for TXA

The indications of TXA are very diverse and the most important ones are presented here. Since 2006, anti-fibrinolytic selection in cardiac surgery has changed from aprotinin to TXA and ε-ACA due to concerns that aprotinin may be associated with an increased risk of heart or brain complications as well as renal failure [47]. Mangano et al. [47] reported that aprotinin is related to increase mortality compared to control, TXA and ε-ACA. The main purpose of using TXA is to reduce postoperative bleeding and the need for blood transfusion in cardiac and non-cardiac surgeries [16]. There are clear benefits in this regard, both in terms of mortality and in terms of economic costs. In a recent meta-analysis, there is strong evidence that TXA reduces the risk of blood transfusions by 38% [48]. Similarly, a study of the effect of antifibrinolytics on blood loss and blood transfusion showed that TXA significantly reduced blood transfusion by 39%, indicating an absolute risk reduction (ARR) of 18%. However, TXA was not associated with a reduction in mortality in all surgeries [25]. The effect of TXA in major pediatric surgery is the same as that found in the adult population. A study [49] of pediatric patients undergoing cardiac surgery showed that TXA significantly reduced blood loss and reduced blood transfusion during surgery as well as within 48 hours. A systematic review [50] concluded that in pediatric spinal surgery, TXA reduces blood loss and the need for blood transfusions. Basta et al. [51] conducted a systematic review and found that antifibrinolytics reduce blood loss and volume of transfusions, especially in cranial and facial surgery.

Other indications for TXA are including orthopedic surgery, topical use, trauma, neurosurgery, etc. Reducing blood loss is very important in orthopedic surgeries, especially in hip or knee arthroplasty and spine surgery. The use of anti-fibrinolytics in orthopedic surgery is supported by a meta-analysis by Kagoma et al. [52], which showed a reduction in blood loss and a relative risk of blood transfusion. The results of a large retrospective analysis by Poeran et al. [53] showed that patients receiving TXA had lower blood transfusions, fewer thromboembolic events, acute renal failure and comorbidities. In a study by Zhang et al. [54], intra-articular injection of TXA in knee arthroplasty reduced blood loss (396 ml) and reduced the risk of blood transfusion (15.4%). The use of TXA in trauma is supported by strong clinical evidence [55, 56]. Extensive studies have examined other indications of TXA [13, 41].

Dosage and Complications:

Different doses of tranexamic acid have been suggested in various studies [57]. In previous cardiac surgery studies, the initial trial dose of TXA was reduced from 100 mg / kg IV to 50

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mg / kg due to seizures during the postoperative period [58]. Similarly, based on previous studies, a prospective cohort study performed in 8929 patients showed that a dose of TXA greater than 100 mg / kg was independently associated with an increased risk of seizures [59]. The results of a retrospective cohort analysis of 11,529 patients with a history of cardiopulmonary bypass surgery showed that seizures was a significant outcome, especially in patients with risk factors such as age, preoperative neuropathy, and cardiovascular disease [60]. According to these results a few centers use moderate or high dose of TXA because of seizure activity. The occurrence of such complications is associated with renal dysfunction. TXA excreted through the kidneys with case reports showing that the patient treated with TXA increased myoclonic motility with increasing periods of general seizures [37, 38]. In a retrospective analysis of 12,000 patients undergoing cardiopulmonary bypass surgery, low-dose TXA was associated with a lower incidence of seizures [61]. Further documentation on the reduction of seizures in the use of low-dose TXA is shown in an extensive meta-analysis in 2019 [62]. Reducing the dose of TXA ensures a reduction in seizures after heart bypass surgery. Dose reduction in oral and intravenous formulations should be performed depending on serum creatinine measurements [13].

Despite recent pharmacokinetic studies in the pediatric population, the ideal dose of TXA in pediatric heart surgery is still unknown [63, 64]. In vitro studies in neonates have shown that plasma concentrations are significantly lower (6.5 μg / ml vs. ~ 17 μg / ml), which is required to prevent hyperfibrinolysis compared to adults [64]. The use of TXA antifibrinolytics prescribed at doses between 10 - 15 mg / kg in orthopedic surgery was reported in a meta-analysis and also reported that increasing the TXA dose (no, <1 g, 2 g and 3 g <), was related to decreased the risk of blood transfusion, however the risk of complications did not increase significantly [41]. The results of a meta-analysis [65] show that the use of 2 g < of topical TXA leads to a significantly lower blood transfusion requirement. The use of tranexamic acid during anesthesia in cardiac surgery did not cause any particular side effects [29].

Recently, a TXA dose-response relationship has been suggested as a modifiable risk factor for seizures in patients undergoing heart surgery [66]. It is now clear from the current literature that moderate to high doses of TXA in cardiac surgery are associated with an increased risk of seizures [66, 67]. Sharma et al. [68], with multivariate analysis of more than 11,000 patients after cardiac surgery, reported that TXA was an independent and robust predictor of the development of generalized postoperative seizures. In addition, patients with seizures had a 2.5-fold higher mortality rate. There are different dose ranges for different uses as indicated by clinical trials.

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Dowd et al [70] recommended the following dose to achieve complete inhibition of fibrinolysis in cardiac surgery: a loading dose of 30 mg per kg, maintenance infusion at 16 mg per kg per h with an additional 2 mg per kg in the circuit). In general, cumulative evidence suggests that TXA is a tolerable drug that is administered orally, intravenously, or topically. Gastrointestinal disorders, skin allergic reactions, visual disturbances are more common and seizures are less likely to occur at high concentrations [39].

Summary of studies related to the use of TXA

TXA has a strong pharmacological and clinical context as an anti-fibrinolytic therapy used in surgery. Administration of TXA should be based on clinical judgment, with guidance on patient history, thromboelastometry, laboratory and radiological examinations, and appropriate to the treatment site and intervention and injection capacity. A review of the literature shows that TXA prevents bleeding in many clinical cases without increasing the risk of thrombosis and has a wide range of clinical applications. Extensive studies have summarized the results of use and therapeutic doses [13, 33, 41], the recent studies in this regard are presented in Table 1. In our previous study (by Negargar et al. [71] using a dose of 20 mg/kg of TA (Tranexamic Acid) pre and post-pump, investigated the effects of TXA on bleeding after coronary artery bypass graft surgery. Our results indicated that administration of TXA before cardiopulmonary bypass does not lead to a reduction in the need for transfusion as compared to the post-pump administration of TXA [71]. It is difficult to draw definitive conclusions about the clinical application of TXA in conditions that have not been well studied. The risk of thrombosis is a major concern in the use of TXA, although a recent meta-analysis concluded that thrombosis was not significantly increased by TXA [62]. The most prominent associated side effect is seizures. So that high rate of seizures lead to a reduction in the dose of TXA in coronary artery bypass graft surgery. However, seizures was uncommon at doses used in most clinical scenarios [32]. The proposed mechanism which TXA leads to seizures is not understood fully but probably involves the TXA molecule acting on hippocampal γ-amino butyric acid type A and glycine receptors (common antiepileptic therapy targets) in a disinhibiting manner [72]. Due to the contradictory results of various studies on the use of this drug in reducing bleeding as well as reducing the need for blood transfusions in patients undergoing surgery, it is recommended to conduct the extensive studies on the dosage of TXA, the safety and overall efficacy, reduce the risk of seizures and thromboembolism, and review of the results of TXA in new clinical uses.

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