

Use of Antifibrinolytic Drugs In Primary Total Knee Arthroplasty

Lara LMC*, Esquivel MLT, Cabrera NGL, Galindo AME, Chavez BIG and Rios DP

Department of Anesthesiology, University Hospital "Dr. Jose E. Gonzalez", Universidad Autonoma de Nuevo Leon, Monterrey, Nuevo Leon, Mexico

Volume 3 Issue 3- 2020

Received Date: 26 Sep 2020

Accepted Date: 13 Oct 2020

Published Date: 16 Oct 2020

2. Keywords

Antifibrinolytic; Hemorrhage; Knee surgery; Total knee arthroplasty; Tranexamic acid

1. Abstract

Total knee replacement is an excellent option for patients with painful arthritis and is recognized as the most cost-effective surgery. It is one of the most common surgeries used to treat end-stage degenerative knee disease, which is almost always accompanied by joint pain, deformity, and motor dysfunction. The use of tranexamic acid in primary total knee replacement with cemented implants is supported by studies with a level of evidence confirming its efficacy in reducing blood loss. In general, the main concern around the use of TXA and other antifibrinolytics is the possibility of an increased risk of thrombotic events, since venous thromboembolic events have been observed immediately after major orthopedic surgery, and TXA could increase this risk.

3. Introduction

Total Knee Arthroplasty (TKA) is an excellent option for patients with painful arthritis and is recognized as the most cost-effective surgery [1]. During and immediately after major orthopedic surgery, a hyperfibrinolytic phase is observed, leading to increased bleeding. Following stimuli such as vascular hypoxia, hypotension, or cytokine circulation, the endothelium releases tissue plasminogen activator, which in turn catalyzes the conversion of plasminogen to plasmin, resulting in the degradation of fibrin and the destruction of blood clots [2] however, the procedure is associated with substantial blood loss, often leading to acute anemia and blood transfusion. This increases the risk of postoperative infection, delayed functional recovery, prolonged hospital stay, and even mortality [3].

The use of Tranexamic Acid (TXA) in primary total knee replacement with cemented implants is supported by studies with a level of evidence confirming its efficacy in reducing blood loss [4] and has become the strategy most popular of the blood preservation of orthopedic surgeons today, reduces transfusions in the TKA by 10-60% depending on the initial transfusion rate [1].

The use of a tourniquet in the TKA has been implicated as the cause of increased fibrinolysis. Therefore, drugs that counteract fibrinolysis, including TXA, could have a potential beneficial role in these procedures [5].

4. Epidemiology

With the aging of the population, the incidence of joint osteoarthritis is increasing. TKA is one of the most common surgeries used to

treat end-stage degenerative knee disease, which is almost always associated with joint pain, deformity, and motor dysfunction [1].

More than 500,000 TKA take place each year in the UK and the US. Approximately 400,000 primary TKA were conducted in China in 2015, a number that has increased between 25% and 30% per year. However, the procedure is associated with substantial blood loss and a high risk of postoperative allogeneic blood transfusion [6]. Transfusion rates after primary and revision total knee arthroplasty range from 4% to 64%, with some reports citing a transfusion rate of up to 93% after bilateral total knee arthroplasty [1, 7].

5. Transfusions

TKA is usually performed with a tourniquet [8]. Average blood loss after total knee replacement has been found to range from 1450 to 1790 mL, leading to anemia and possibly the need for blood transfusion [7]. This significant amount of blood loss leads to swelling, bruising, postoperative stiffness, and possible prolonged drainage, delaying rehabilitation, functional recovery, and discharge from the hospital, increasing health care costs, which often leads to acute anemia and blood transfusion [1]. The leading cause of postoperative blood loss after total knee arthroplasty can be attributed to surgical trauma leading to activation of both the coagulation cascade and local fibrinolysis [7].

Blood transfusions are linked to many well-documented complications, including transfusion-related acute lung injury, hemolytic transfusion reactions, postoperative infections, and longer hospital stays [9]. Although the infectious and immunosuppressive risks of blood transfusions have decreased in recent years, they still persist

*Corresponding Author (s): Luz Mabel Cardenas Lara, Department of Anesthesiology, University Hospital "Dr. Jose E. Gonzalez", Universidad Autonoma de Nuevo Leon, Av. Francisco I. Madero s/n, Col. Mitras Centro, CP. 66460, Monterrey, Nuevo Leon, Mexico, Email: rodolfo159@hotmail.com

[5]. In addition to the risk of transfusion-associated complications, patients who undergo joint replacement and receive allogeneic red blood cell transfusions incur a higher cost of care. The cost of activities related to blood and transfusions for surgical patients has been reported up to \$ 1,200 per unit transfused. Decreasing blood transfusion rates limits patients' risk of adverse outcomes and reduces surgical costs, making blood-conserving practices a necessary component of any surgical protocol [9]. Consequently, it is crucial to identify effective methods to minimize perioperative blood loss and reduce the rate of blood transfusion, indicating the need for a critical review of blood conservation practices to optimize operational costs and patient results [1].

6. Pharmacology

TXA is a competitive inhibitor of plasminogen activation that interferes with fibrinolysis [10]. It binds reversibly to the lysine binding site of plasminogen, inhibiting fibrin binding and plasmin activation [2]. The half-life of TXA is approximately 80 min, provided that renal function is normal, so dose adjustments are recommended in patients with renal failure [5]. The studies reported that fibrinolysis peaked six hours after TKA and lasted for approximately 18 hours after the operation [3].

Recent research showed that multiple boluses of intravenous TXA further reduced blood loss, inflammation, and fibrinolysis without increasing the risk of complications after TKA. [3] A 15 mg / kg bolus appears to be sufficient and is the most used [2].

7. Route of Administration

Oral and topical applications of TXA have been used perioperatively, but most studies use intravenous TXA [5]. Multiple studies have shown that intravenous administration of TXA reduces postoperative bleeding and blood transfusions [4, 11]. Sustained intraoperative TXA infusion up to 16 hours postoperatively can help limit blood loss and transfusion needs, as preliminary studies show [2]. Intravenous administration results in rapid diffusion of TXA into the synovial fluid of the target joint, but topical intra-articular administration achieves the same result without wide systemic distribution, potentially reducing thromboembolic risk [12]. TXA intravenously: 10 mg/kg, some authors administer 1000 mg per dose IV. Followed by an infusion of 1 mg/kg/hour. Dissolution in 100 to 250 ml of physiological solution. The first dose is recommended to be administered two hours prior to surgery [9].

Although blood loss prevention protocols have been adopted in many institutions, there are concerns regarding intravenous administration of TXA in some settings, and topical administration may be considered an attractive alternative that is potentially less risky than systemic administration [12]. Topical application of TXA to the knee joint before closure. While topical application of TXA has been shown to be a simple and cost-effective way to re-

duce blood loss in dental, cardiac, and spinal procedures, less data is available regarding total knee replacement [7]. Recent clinical trials to confirm the safety and efficacy of the administration of TXA as a single topical intra-articular dose have been promoted by topical administration of TXA in dental surgery even in patients receiving oral anticoagulation [12]. 1000 mg diluted in 100 ml of physiological solution, usually 1 or 2 doses. The first one prior to placing the trial components, and the second at the end of the placement of the final components.

However, in the current climate of tightening healthcare budgets and the debate around fiscal austerity, the implications of the growing demand for TKA have led to intense discussion about the profitability of a new method of managing TXA. Although the cost-benefit advantage of oral TXA has been demonstrated in previous studies, only one prospective randomized trial of oral TXA in TKA has been reported [6]. Oral TXA: It varies between 1000 and 1300 mg. Generally, 1 dose preoperative and 2 to 3 postoperative [1].

8. Complications

The safety of TXA can be affected by its bio distribution. Formal contraindications to intravenous TXA include a history of a thromboembolic or ischemic event such as pulmonary embolism, deep vein thrombosis, ischemic stroke, acute myocardial infarction, or ischemic retinopathy [7, 12]. In general, the main concern around the use of TXA and other anti-fibrinolytics is the possibility of an increased risk of thrombotic events, [5] since venous thromboembolic events have been observed immediately after major orthopedic surgery, and TXA could increase this risk [2]. The adverse effects of TXA are rare and mainly limited to nausea, generally caused by a rapid intravenous injection [4].

9. Clinical Outcomes

The recent meta-analysis by Shan et al included 19 studies and reported mid- and long-term postoperative quality of life scores that were better than preoperative ones, with a satisfaction rate of 75% at 5 years [13]. Participation in increasing quality of life is strongly correlated with patient motivation [14].

Some patients are dissatisfied with the outcome of their TKA, despite correct implant alignment, optimal implant size, and satisfactory ligament balance. Patient satisfaction is strongly correlated with their ability to carry out activities of daily living. Going up and down stairs, getting in and out of a vehicle, walking and standing, rolling sideways and bending over are activities correlated with the patient's preoperative expectations. These functional expectations are particularly important in young and athletic patients [15].

10. Comparison with E-aminocaproic Acid

TXA is a synthetic lysine analog and acts as an anti-fibrinolytic agent just like e-aminocaproic acid (ϵ -ACA) [4]. The anti-fibrino-

lytic potency of TXA is 6 to 10 times higher compared to ϵ -aminocaproic acid [4]. Previous studies have confirmed the use of intravenous TXA comparing it with aminocaproic acid with similar results in terms of total blood loss and transfusion rate after TKA [16-18]. One study showed that the oral use of aminocaproic acid is similar to its TXA counterpart in evaluating parameters in the present study. Although patients in the TXA group averaged 140 ml less blood loss than patients in the ϵ -ACA group, this difference did not appear to be clinically important; The transfusion rates were very low and there were no differences between the groups in postoperative complications, therefore the results indicated that TXA did not have superior blood conservation effects, safety profile or differences in functional scales compared to ϵ -ACA in the TKA. The use of multiple doses of oral aminocaproic acid at the selected dose was considered effective and cost-effective as a standard protocol to achieve less blood loss and a lower rate of transfusion and medication-related adverse events in patients undergoing primary total knee replacement [1].

ϵ -ACA, like TXA, can be administered in three ways at their respective doses. ϵ -ACA intravenously: 100 to 150 mg/kg followed by an infusion of 10-15 mg/kg/hour. Oral ϵ -ACA: 5 grams per dose (there are 500 mg and 1000 mg tablets), the administration of 1 preoperative oral dose of 2 grams and two postoperative doses of 2 grams showed that there are no differences with respect to the administration of TXA in conventional doses [1]. Topical ϵ -ACA: 5 grams of AAC diluted in 100 ml of physiological solution left in the wound for 3 minutes [19].

11. Conclusions

The prophylactic use of TXA for knee and hip arthroplasty can be used effectively during practice. This could result in a significant reduction in intra- and postoperative blood loss, as well as consecutive allogeneic blood transfusions. However, if a prophylactic strategy should be applied to all patients who undergo elective arthroplasty of large joints, or if in the future stratified concepts that consider the underlying disease, baseline hemoglobin values, and probabilities of local transfusion, it is necessary to clarify in further studies.

It is important to consider the contraindications and risks, included in a broader concept of patient blood management. The initial results of different studies suggest that the administration of TXA may be a factor in complications such as thromboembolic or ischemic events such as pulmonary embolism, deep vein thrombosis, ischemic stroke, acute myocardial infarction or ischemic retinopathy.

References

1. Morales-Avalos R, Ramos-Morales T, Espinoza-Galindo AM, Garray-Mendoza D, Peña-Martinez VM, Marfil-Rivera LJ, et al. First

Comparative Study of the Effectiveness of the Use of Tranexamic Acid against ϵ -Aminocaproic Acid via the Oral Route for the Reduction of Postoperative Bleeding in TKA: A Clinical Trial. *J Knee Surg.* 2019.

2. Blanié A, Bellamy L, Rhayem Y, Flaujac C, Samama CM, Fontenay M, et al. Duration of postoperative fibrinolysis after total hip or knee replacement: a laboratory follow-up study. *Thromb Res.* 2013; 131(1): e6-e11.
3. Cao G, Huang Q, Huang Z, Zhang S, Luo Z, Lei Y, et al. The efficacy and safety of multiple-dose oral tranexamic acid on blood loss following total hip arthroplasty: a randomized controlled trial. *Int Orthop.* 2019; 43(2): 299-305.
4. Hiippala ST, Strid LJ, Wennerstrand MI, Arvela JV, Niemelä HM, Mäntylä SK, et al. Tranexamic acid radically decreases blood loss and transfusions associated with total knee arthroplasty. *Anesth Analg.* 1997; 84(4): 839-844.
5. Neilipovitz DT. Tranexamic acid for major spinal surgery. *Eur Spine J.* 2004; 13: S62-S65.
6. Luo ZY, Wang HY, Wang D, Zhou K, Pei FX, Zhou ZK. Oral vs Intravenous vs Topical Tranexamic Acid in Primary Hip Arthroplasty: A Prospective, Randomized, Double-Blind, Controlled Study. *J Arthroplasty.* 2018; 33(3): 786-793.
7. Abdel MP, Chalmers BP, Taunton MJ, Pagnano MW, Trousdale RT, Sierra RJ, et al. Intravenous Versus Topical Tranexamic Acid in Total Knee Arthroplasty: Both Effective in a Randomized Clinical Trial of 640 Patients. *J Bone Joint Surg Am.* 2018; 100(12): 1023-1029.
8. Iwai T, Tsuji S, Tomita T, Sugamoto K, Hideki Y, Hamada M. Repeat-dose intravenous tranexamic acid further decreases blood loss in total knee arthroplasty. *Int Orthop.* 2013; 37(3): 441-445.
9. Churchill JL, Puca KE, Meyer ES, Carleton MC, Truchan SL, Anderson MJ. Comparison of ϵ -Aminocaproic Acid and Tranexamic Acid in Reducing Postoperative Transfusions in Total Hip Arthroplasty. *J Arthroplasty.* 2016; 31(12): 2795-2799.
10. Yang ZG, Chen WP, Wu LD. Effectiveness and safety of tranexamic acid in reducing blood loss in total knee arthroplasty: a meta-analysis. *J Bone Joint Surg Am.* 2012; 94(13): 1153-9.
11. Kagoma YK, Crowther MA, Douketis J, Bhandari M, Eikelboom J, Lim W. Use of antifibrinolytic therapy to reduce transfusion in patients undergoing orthopedic surgery: a systematic review of randomized trials. *Thromb Res.* 2009; 123(5): 687-96.
12. Gomez-Barrena E, Ortega-Andreu M, Padilla-Eguiluz NG, Pérez-Chrzanowska H, Figueredo-Zalve R. Topical intra-articular compared with intravenous tranexamic acid to reduce blood loss in primary total knee replacement: a double-blind, randomized, controlled, noninferiority clinical trial. *J Bone Joint Surg Am.* 2014; 96(23): 1937-1944.
13. Shan L, Shan B, Suzuki A, Nouh F, Saxena A. Intermediate and Long-Term Quality of Life After Total Knee Replacement: A Systematic Review and Meta-Analysis. *J Bone Joint Surg Am.* 2015; 97: 156-68.
14. Canovas F, Dagneaux L. Quality of life after total knee arthroplasty. *Orthop Traumatol Surg Res.* 2018; 104(1S): S41-S46.
15. Nakahara H, Okazaki K, Mizu-Uchi H, Hamai S, Tashiro Y, Matsuda S, et al. Correlations between patient satisfaction and ability to per-

form daily activities after total knee arthroplasty: why aren't patients satisfied? *J Orthop Sci.* 2015; 20: 87-92.

16. Boese CK, Centeno L, Walters RW. Blood conservation using tranexamic acid is not superior to epsilon-aminocaproic acid after total knee arthroplasty. *J Bone Joint Surg Am.* 2017; 99(19): 1621-1628.
17. Churchill JL, Toney VA, Truchan S, Anderson MJ. Using aminocaproic acid to reduce blood loss after primary unilateral total knee arthroplasty. *Am J Orthop.* 2016; 45(5): E245-E248.
18. Liu Q, Geng P, Shi L, Wang Q, Wang P. Tranexamic acid versus aminocaproic acid for blood management after total knee and total hip arthroplasty: a systematic review and meta-analysis. *Int J Surg.* 2018; 54: 105-112.
19. Harper RA, Sucher MG, Giordani M, Nedopil AJ. Topically applied epsilon-aminocaproic acid reduces blood loss and length of hospital stay after total knee arthroplasty. *Orthopedics.* 2017; 40(06): e1044-e1049.