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The Hemostatic Effect of Tranexamic Acid during and after Total Knee Arthroplasty

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ABSTRACT

Introduction:
Total knee arthroplasty (TKA) is an effective treatment method for end-stage knee osteoarthritis, and with the aging population, the demand for this surgery has significantly increased. However, bleeding during and after TKA remains a major complication. Blood transfusion, while necessary in some cases, is associated with various complications. Therefore, finding measures to reduce the need for transfusion is crucial in minimizing postoperative complications.

Materials and Methods:
This study was conducted to review the world literature on The Hemostatic Effect of Tranexamic Acid during and after Total Knee Arthroplasty. In this review study, the terms total knee arthroplasty and tranexamic acid were searched in the title and abstract of articles published in internationally recognized scientific databases, and all English and related articles were listed.

Result:
Tranexamic acid, an antifibrinolytic agent, has shown promising results in reducing blood loss in major surgeries such as TKA. Different administration methods of tranexamic acid have been deemed effective, with the choice depending on the surgical team's preference and protocol.

Discussion:
Several studies have demonstrated the efficacy of tranexamic acid in reducing bleeding during and after TKA, leading to a decreased need for blood transfusion and its associated complications. Additionally, tranexamic acid has been found to improve joint function post-surgery in TKA patients. Overall, tranexamic acid represents a valuable option in managing bleeding in TKA procedures, offering potential benefits in reducing transfusion requirements and improving patient outcomes.

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Introduction

Bleeding is a significant complication of surgery. In certain instances, surgical bleeding can be facilitated by structural anomalies, recent drug intake, or coagulopathies (1). Uncontrolled bleeding can lead to an elevated risk of infection, ischemic events, mortality, and complications associated with blood transfusion (2).

Total knee arthroplasty (TKA) is widely used as an effective surgical treatment for end-stage osteoarthritis and other knee joint diseases to reduce pain and improve a patient's quality of life (3). The demand for this surgical method has substantially increased over the past few decades, primarily attributed to the aging population, rising obesity rates, and a more active lifestyle (4). From 2010 to 2012, there were 52.5 million diagnosed cases of osteoarthritis in the United States adult population, accounting for 22.7% of all adults. Among them, 22.7 million adults (9.8%) experienced limitations in their daily activities due to osteoarthritis. By 2040, these numbers will rise to 78.4 million people (25.9% of the total adult population) and 34.6 million adults (11.4%). Bleeding during and after surgery is a common occurrence in invasive surgical procedures, including orthopedic surgery (5).

The amount of blood lost in total during a TKA procedure can exceed two liters (6). TKA is known to increase the likelihood of requiring a blood transfusion, which in turn increases the risk of transfusion-related complications such as reactions, infections, fluid overload, and altered mental status (7).

Implementing strategies to minimize bleeding and decrease blood transfusion rates has improved surgical outcomes and reduced healthcare costs (6). Several studies have investigated different approaches to reduce post-TKA bleeding, leading to the proposal of effective methods. These methods include drain clamping (8), local application of Floseal, a blood coagulant matrix including thrombin and gelatin, topical fibrin sealant, epinephrine, and tranexamic acid (TA) (8-11). TA as an indirect inhibitor of fibrinolysis can be traced back to the early 1960s when it was first published by the laboratory of Shusuke and Otaku Okamoto (12). Initially, it was prescribed for women with heavy menstrual bleeding and patients with hereditary bleeding disorders (12). However, its application quickly expanded to selective surgeries due to its blood-saving ability (12). There are only a few contraindications for using TA, with the most important ones being continuous venous or arterial thrombosis and drug allergies. Doses should also be adjusted in cases of renal failure (12).

Mechanism of action

TA is a synthetic derivative of the amino acid lysine. It functions as an antifibrinolytic agent by binding to plasminogen and preventing its interaction with fibrin. It ultimately hinders the dissolution of fibrin clots (13). TA is available in intravenous and oral formulations. In healthy volunteers, the intravenous half-life of TA has been reported to be two hours (14). Also, food intake does not affect the time required to reach the maximum concentration (14).

The bioavailability of TA, both oral and intravenous, is reported to be around 33-34% (14). The excretion of the intravenous form of TA follows an exponential pattern, with approximately 90% of the drug being excreted through urine within 24 hours. This issue is relevant to the increased complications associated with TA in patients with renal dysfunction. Depending on serum creatinine measurement, dosage reduction should be considered for oral and intravenous formulations (14).

TA in post-TKA hemostasis

TKA is linked to a higher demand for blood transfusions, leading to an increased risk of blood transfusion-related complications, including transfusion reactions, infections, fluid overload, and alterations in mental status (7). TA has been shown to reduce the need for blood transfusion in patients undergoing TKA, significantly decreasing the proportion of patients who need this procedure (15). This method has been successfully used in orthopedics, particularly in TKA, to minimize postoperative blood loss (16). The implementation of TA is expected to decrease total blood loss and significantly

increase postoperative hemoglobin levels, reducing blood transfusion rates (17). The preferred administration methods vary among surgical teams, with topical and intravenous routes demonstrating efficacy. The specific surgery type and anatomical location influence decision-making (16).

TA can be administered through various routes, including topical, intravenous, oral, and intramuscular. The time it takes to achieve maximum plasma concentration differs depending on the administration method. Oral administration takes approximately 2 hours, intramuscular administration takes about 30 minutes, and intravenous administration takes 5 to 15 minutes. Consequently, the intravenous method is the most suitable for rapidly increasing the therapeutic concentration of TA (18).

Comparison between intravenous and topical routes

Intravenous administration of TA has been shown to effectively reduce blood loss and the need for blood transfusion rate in patients undergoing TKA without increasing the risk of deep vein thrombosis (19). Likewise, the local application of TA can effectively reduce bleeding volume and decrease the need for blood transfusions without increasing the risk of thromboembolic events (20). The appropriate dose for achieving these benefits and minimizing the risk of deep vein thrombosis is typically one to three doses of intravenous TA. Additionally, topical administration of TA has been found to reduce postoperative swelling and associated pain (18).

Topical application of TA can significantly reduce blood loss volume. One advantage of topical TA is the potential for reduced postoperative swelling, leading to decreased pain (21). There is no difference in the level of Plasmin-Alpha-2-Antiplasmin (PAP) complex (an index of recent antifibrinolytic activity) in blood and wounds between intravenous administration of a single dose and topical administration of TA. However, administrating a second intravenous dose increases the PAP level more than topical application (22). Moreover, there is no significant variation in the levels of Prothrombin Fragment 1.2 and, consequently, the extent of thrombin formation between the two groups. Given that we can attain the appropriate therapeutic concentration with the local application of TA and there are no substantial differences in the mechanism of action, coagulation, and fibrinolytic profile compared to intravenous administration, utilizing topical TA emerges as a more convenient alternative, especially when considering the safety concerns associated with intravenous administration (22).

In a study conducted in 2017, patients were divided into three groups: local, intravenous injection, and control. In the local group, 1.5 grams of TA diluted in 50 ml of normal saline was applied to the entire surgical site before opening the tourniquet. It was allowed to absorb completely for 5 minutes. The intravenous injection group received 20 mg/kg of TA diluted in 100 ml of 0.9% saline solution during anesthesia for 10 minutes. The control group received only 100 ml of saline during anesthesia for 10 minutes. The volume of blood loss in the intravenous group was lower than in the local group, but the local use was still effective in reducing the need for blood transfusion without the possible complications of intravenous administration (23).

In a 2018 study, one group of patients received 1 gram of intravenous TA before tourniquet inflation and another gram at closure, while the other group received 3 grams of TA diluted in 45 ml of normal saline, applied topically. The group that received topical TA exhibited significantly higher blood loss volume and drain output than the intravenous TA group. However, the two groups had no significant difference in the risk of thrombotic events between (24).

In another study, patients were divided into two groups. One group received 10 mg/kg of TA ten minutes before closing the tourniquet, while the other group received 1 gram of TA diluted in 50 ml of normal saline and injected into the surfaces of the surgical site. There was no significant difference in total blood volume loss between the two groups (24).

Simultaneous intravenous and local administration

The volume of blood loss after simultaneous intravenous and local administration of TA is

not significantly different from that after each alone (25). Intravenous administration of TA can increase hidden blood loss due to tourniquet closure in TKA and intensify fibrinolytic activity at the site. When applied before wound closure, topical TA can be rapidly absorbed and remain in place with a half-life of three hours. When compared to the use of local or intravenous TA alone or the control group, the combined use of local and intravenous TA can reduce total blood loss and the need for blood transfusion c

In 2021, a study evaluated the synergistic effect of intravenous and topical TA. One group of patients received a combination regimen, including an intravenous injection of one gram of TA 30 minutes after skin incision and local application of three grams of TA diluted in 45 ml of normal saline solution after washing the surgical site and before closing it. Another group received one gram of TA intravenously 30 minutes after the skin incision, followed by an additional gram after surgery and three hours after the first dose. The combination regimen and the two-dose regimen of intravenous TA had similar effects in reducing the volume of blood loss and the need for transfusion (26). A meta-analysis in 2017 showed that the combined use of intravenous and topical TA can have a greater effect on reducing blood volume loss than the administration of intravenous TA alone (27).

Oral administration

Oral TA can effectively reduce hemoglobin drop, blood loss volume, and the need for blood transfusion. Due to its effectiveness and cost benefits, oral TA is useful for TKA (28). In a 2013 study, which compared the bleeding volume 12 and 24 hours after surgery and the hematocrit 24 hours after surgery between two groups, only one of which received oral TA, it was found that oral administration of TA significantly reduced bleeding volume and hematocrit drop after TKA surgery (29).

In a 2017 study, three different methods of TA administration were compared. One group received two doses of 20 mg/kg intravenous TA, the second group received three grams of topical TA, and the third group received two doses of 20 mg/kg of oral TA. There was also a control group. All three administration methods resulted in a significant decrease in the amount of hemoglobin drop and the need for blood transfusion. Based on this study, oral TA is recommended because it has the same clinical value as the other two methods (30). A study conducted in 2019 indicated that the oral regimen of TA (which consists of a one-gram dose two hours prior to surgery, followed by another dose two hours and a final dose six hours post-surgery can be just as effective as the oral/injectable/local regimen. The study also found no significant difference in blood loss between the two groups. However, the oral regimen offers the added benefits of reducing healthcare costs and relieving nurses from additional burdens without affecting the outcome of patient treatment (31).

Materials and Methods

This article used data from the well-reputed databases PubMed, Science Direct, and Google Scholar. The data were collected through research and review articles on The Hemostatic Effect of Tranexamic Acid during and after Total Knee Arthroplasty, which were summarized to form an improved review article. The following keywords were used to search the databases: tranexamic acid and total knee arthroplasty. The research texts are from 2013 to 2023.

Result

Numerous studies have explored strategies to control bleeding during and after TKA. Tranexamic acid, an antifibrinolytic agent, has shown promising results in reducing blood loss in major surgeries such as TKA. Different administration methods of tranexamic acid, including topical, intravenous, and combined administration of IV and topical tranexamic acid, have been reported effective, depending on the surgical team's preference and protocol.

Discussion

Numerous efforts have been made to minimize blood loss in patients undergoing TKA surgery. The administration of TA has shown promising results in significantly reducing blood loss without causing complications such as venous or pulmonary thrombosis in this patient population.

There are various routes of TA administration, all of which have been reported to be effective (18). The choice of administration method often depends on the surgical team's preference (16). Comparing the effectiveness of intravenous injection and local use of TA in different studies has yielded varying results based on dosage and application method. Some studies have found intravenous administration more effective in reducing blood loss volume, while others have found local administration more effective. In certain studies, both methods have shown similar effects. The synergistic effect of concurrently using intravenous and topical TA has been confirmed in some studies. Due to the limited sample size of randomized controlled trials, further research is necessary. The oral administration of TA can be just as effective as other methods in reducing blood loss volume during TKA. Furthermore, due to its cost-effectiveness, it is highly recommended for use in TKA surgery.

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