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Review Article

INTRA-ARTICULAR TRANEXAMIC ACID PLUS DRAIN CLAMPING IN TOTAL KNEE ARTHROPLASTY: REVIEW

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ABSTRACT

Total knee arthroplasty also known as total knee replacement is a major orthopedic surgery in which parts of the knee joint are replaced with prostheses. Knee replacement can relieve pain and allow people to stay active. Total knee arthroplasty can be associated with significant amount of blood loss and blood loss related multiple complications. Reduction in blood loss and its complications is one of the challenging of this surgery. To overcome and minimize the blood loss and its resulting complications, there has been a focus on pharmacological agents. Among the pharmacological agents, tranexamic acid is being used widely. Tranexamic acid is a synthetic analog of the amino acid lysine which serves as an anti-fibrinolytic agent. There are several advantages for using tranexamic acid in total knee arthroplasty. There are various routes through which tranexamic acid can be administered. Intra-articular tranexamic acid application plus drain clamping has recently become one of the most popular blood conservative methods in total knee arthroplasty.

Key words: Total knee arthroplasty (TKA); Tranexamic acid (TXA); Intra-articular (IA); Drain-clamping

INTRODUCTION

Total knee arthroplasty (TKA) is a major orthopedic surgery that is associated with significant amounts of blood loss. The significant blood loss post-TKA has been reported to range from 700 mL to 1700 mL [1-4]. Increased bleeding may result in complications and even may necessitate blood transfusion. Intra-operative and post-operative blood loss is however an unavoidable complication of the surgery [5-7]. The complications associated with increased blood loss are postoperative pain, hematoma and seroma formation, arthrofibrosis, persistent bleeding [8, 9], knee joint swelling, knee motion restriction, delayed recovery [10] and increased healthcare cost due to longer hospital stay [11, 12]. Blood transfusion is not the solution so reducing blood loss remains a major concern among the surgeons. The risk of blood transfusion and the strategies proposed for allogeneic blood transfusions (ABTs) reduction is listed below with respective heading.

There has been a focus on pharmacological agents, such as aprotinin, ε-aminocaproic acid, and tranexamic acid (TXA), to decrease blood loss through the inhibition of clot degradation [13]. Among all these agents, use of tranexamic acid has been vastly studied and has shown to decrease post-operative blood loss and requirement of blood transfusion [14-20]. The advantages of tranexamic acid are its cost effectiveness, it decreases the need for blood transfusions and the administration is simple [21].

Tranexamic acid is a synthetic anti-fibrinolytic agent that inhibits the activation of plasminogen to plasmin by blocking the lysine-binding sites of plasminogen to fibrin, which results in prevention of fibrinolysis. Consequently, there is a decrease in proteolytic action on the fibrin monomers and fibrinogen, which ultimately results in clot stabilization and reduces blood loss [22]. TXA can be applied by various routes including intravenous (IV), intra-articular, oral and intramuscular [23]. However, the ideal route of TXA administration remains controversial [24-27].

The effect of TXA on blood loss lasts for 7-8 hours in serum and for a longer period in tissue [28-31]. According to Mannucci et al [32], tranexamic acid inhibits tissue fibrinolysis for up to 17 hours and consequently stabilizes the possibility of clots entering the extravascular space and accumulating in tissues. For patients undergoing TKA, IV route is the best for rapidly increasing and maintaining the therapeutic concentration [23]. Then, an increasing number of studies began to pay close attention on the effect of IV TXA on TKA [33, 34].More importantly, adverse effect noted is thromboembolic complications, such as deep vein thrombosis (DVT) and pulmonary embolism (PE). But few published literatures stated that there is no risk of postoperative complication such as DVT or PE and treatment with TXA is safe [35, 36]. It is generally accepted, that only a fraction of intravenously injected TXA reaches the target location [29]; that up to 95% of the drug can be eliminated in the urine; and that in patients with impaired kidney function, the dosage needs to be corrected [37]. Thus, safe way of using TXA is a concern among surgeons. There has been a growing interest in using TXA as an IA agent in total knee replacement. The purpose of this study was to study the efficacy of

intra-articular tranexamic acid administration plus drain clamping in total knee arthroplasty.

Strategies proposed for allogeneic blood transfusions (ABTs) reduction [38]:

The three pillars (pre-operative, intra-operative and post-operative) of patient's blood management and saving

1. **Pre-operative**
   - ❖ Detection of anemia and iron deficiency treatment
   - ❖ Erythropoietin
   - ❖ Perioperative management of antiplatelet agents
   - ❖ Transfusion protocol agreement
   - ❖ Pre-operative autologous blood donation
2. **Intra-operative**
   - ❖ MIS and navigated MIS TKA(MIS: Minimally invasive)
   - ❖ Tourniquet
   - ❖ Hypotensive epidural anesthesia
   - ❖ Acute normovolemic haemodilution
   - ❖ Antifibrinolytic agents
   - ❖ Topical fibrin sealants
   - ❖ Intra-operative cell salvage
   - ❖ Peri/intra-articular (bupivacaine and epinephrine)
   - ❖ Injections
   - ❖ Bipolar vs. monopolar sealant
   - ❖ Platelet-rich plasma
   - ❖ Bone wax
   - ❖ Sealing femoral tunnel
3. **Post-operative**
   - ❖ Compression and cryotherapy
   - ❖ Limb position
   - ❖ Post-operative cell saving
   - ❖ Drainage clamping

Blood transfusion might carry the risk of:

1. Infections [39-41]
2. Immunosuppression [41]
3. Immunological reactions [39, 40, 42-44]

4. Transfusion-related acute lung injury [41]
5. Hemolysis [41]
6. Volume overload [42-44]
7. Renal failure [42-44]
8. Periprosthetic infection [42-44]
9. Prolonged rehabilitation [41]
10. Financial burden on patients [43]
11. High rate of morbidity and mortality [43]

Adverse effects of tranexamic acid:

1. Nausea and vomiting with high dose or injected quickly [45, 46]
2. Hematoma [47]
3. Pulmonary embolism (PE) [15, 48, 49]
4. Deep vein thrombosis (DVT) [10, 15, 49-53]
5. Superficial vein thrombosis [47]
6. Acute kidney injury (AKI) [47]
7. Myocardial infarction (MI) [47]
8. Death (related to cardiac) [47]

OUTCOMES

In Mutsuzaki and Ikeda et al. [14] retrospective study of 140 Patients, study group (n=70) had an intra-articular injection of TXA (1000 mg) and drain clamping for 1 h postoperatively and control group (n=70) were not given TXA and did not undergo clamping of their drains. Author found that total blood loss, total drainage, mean transfusion volume, and transfusion rates were lower in the study group than in controls ($P<0.001$). Hemoglobin levels on post-operative days (PODs) 1 and 14 were similar in the groups, but on POD 7 the hemoglobin level was higher in the study group than in controls ($P<0.001$). D-dimer level on POD 7 was lower in the study group than in controls ($P<0.05$). There were no complications in either group.

Sa-ngasoongsong et al. [15], conducted a triple-blinded randomized controlled study in 135 patients to evaluate the effectiveness and low dose response effect of two doses IA-TXA regimens in conventional total knee replacement (TKR) on blood loss and blood transfusion. The patients were given intra-articular solution as: Control group (physiologic saline), TXA-250 group (TXA 250 mg), and TXA-500 group (TXA 500 mg). The solution was injected after wound closure followed by drain clamping for 2 hours. Author found that mean total hemoglobin loss 2.9 g/dL in control group compared with 2.2 g/dL in both TXA groups ($p> 0.001$). Ten patients (22%, control), six patients (13%, TXA-250) and none (TXA-500) required transfusion ($p= 0.005$). Thromboembolic events were detected in 7 patients (4 controls: 1 symptomatic PE and 3 DVT, 1 TXA-250:

DVT and 2 TXA-500: 2 DVT, p =0.35). Functional outcome was non-significant difference between groups.

Park et al. [20] conducted nonrandomized and retrospective the study on 95 patients with primary osteoarthritis who were to have a unilateral cemented TKR. In group A, the drain was released following tourniquet deflation. In group B, 500-mg TXA was injected into the knee joint via a drain tube after fascia closure and the drain was clamped for the first 30 min to prevent leakage. In group C, the drain was clamped for the first 3-h post-operation. Authors found a significantly lower postoperative total blood loss, drained blood volume, decreasing hematocrit level, and less transfused blood volume in the IA-TXA injection group (group B) and the 3-h drainage clamping group (group C) compared to the conventional negative drainage group (group A; $p < 0.001$). There was no significant difference between groups B and C ($p = 0.99$).

In Chareancholvanich et al. [16] study of 240 patients, Group A or control group, the drain was not clamped and the patient received a placebo; Group B, the drain was not clamped and the patient received tranexamic acid; Group C, the drain was clamped and the patient received a placebo; and Group D, the drain was clamped and the patient received tranexamic acid. The mean postoperative volumes of drained blood and the amount of blood transfusion in the three study groups (group B, C and D) were significantly lower than those in the control group ($p<0.05$), which group D had the lowest values. Furthermore, group B and D could maintain the Hemoglobin level better than group A and C ($p<0.001$). In terms of blood transfusions rate, although the patients in group D required transfusion less than group A and C ($p<0.05$), there was no significant difference between group D and B. The relative risks for transfusion requirement were 4.4 for group A; 1.4 for group B and 3.0 for group C when compared to group D.

DISCUSSION

Hippala et al. [54], was first to describe the benefit of tranexamic acid as anti-fibrinolytic agent to reduce blood loss after knee arthroplasty. Intra-articular tranexamic application has recently become one of the most popular blood conservative methods in total knee replacement (TKR) due to its successfully proven effectiveness on reduction of postoperative blood loss (PBL) and blood transfusion (BT) without significant risk of postoperative complication [19, 30, 55-59]. According to Park et al. [20], there is no guideline for implementing IA-TXA, such as the TXA dosage which varies from 250 to 3000 mg and the optimal drain clamping time after joint injection.

According to the published literatures, TXA plus drain-clamping could decrease the need for transfusion, total blood loss, and blood loss in drainage [14-16, 20]. Mutsuzaki and Ikeda et al. [14] concluded that IA injection of tranexamic acid (1000 mg) retrogradely via the drain at the end of the operation and clamping the drain for 1 hour effectively reduced postoperative blood loss and the need for blood transfusion after cementless TKA compared to control. Roy et al. [60] reported that 500-mg IA-TXA plus 1-h drain clamping

significantly reduced the drain output at 48-h post-operation and blood transfusion after primary unilateral cemented total knee replacement compared to the control group. Sa-ngasoongsong et al. [61] concluded that low dose (250mg) IA-TXA injection, combined with 2-hour clamp drain in patients undergoing computer assisted surgery-TKR was one interesting option in reducing post-operative blood loss by 40-46% and proportion of patients requiring blood transfusion to 13% as compared to placebo. Chareancholvanich et al.[16] concluded that the clamping of drain combined with tranexamic acid administration could reduce postoperative blood loss and blood transfusion after TKA significantly greater than using tranexamic acid or drain clamping alone. Park et al. [20], low-dose (500 mg) IA-TXA plus 30-min drain clamping is advantageous for reducing total blood loss and blood transfusion requirements without thromboembolic complication.

There are several advantages for the use IA-TXA in comparison of IV-TXA such as easy administration, providing a maximum concentration of TXA at the bleeding site and inhibiting local activation of fibrinolysis [62]. The study has confirmed that the administration of TXA, which is used directly into the surgical wound, reduced postoperative bleeding from 20 to 25% [62]. Where the use of IV-TXA is contraindicated (in cases with a history of a thromboembolic or ischemic event such as deep venous thrombosis, pulmonary embolism, acute myocardial infarction, ischemic cerebrovascular accident or ischemic retinopathy [63]), IA-TXA can be thought of but this does not rule out the occurrence of VTE complications. Sa-Ngasoongsong et al. [15] suggested that combining a low-dose IA-TXA (500 mg) with 2-h drainage clamping is effective for reducing postoperative blood loss and transfusion in conventional TKR but the VTE complication (DVT) was noted in the IA-TXA group. Park et al. [20] concluded that the drainage clamping method can be safer than IA-TXA administration in patients with a risk factor of VTE complication. Furthermore, the IA-TXA administration method can be more optimal than drainage clamping in patients with high bleeding tendency or lateral retinacular release during TKR, who would be concerned about postoperative wound complication.

Most of the blood loss in TKR occurs during the first few postoperative hours (37% and 55% at 2 and 4 h, respectively) [64]. Thus, it seems reasonable to clamp the drain tube in the first few hours after TKR to create a tamponade effect for bleeding control. Therefore, the balance between creating a tamponade effect and reducing wound complications is important in patient's prognosis. An optimal protocol for the number of hours needed for drain clamping has not been established [65, 66]. Park et al. [20] assumed that the most critical time zone forming the tamponade effect is 3 h after the operation when most bleeding occurs, and clamping for more than 3 h can lead to increased wound complications.

The most concerning complication regarding drain-clamping is ecchymosis. Chareancholvanich et al [16] reported that TXA plus drain-clamping did not increase the incidence of ecchymosis when compared with the control group or to a group of patients without drain clamping. Tai et al. [66] concluded that there were wound problems such as acute infection, bruising, and severe oozing in 2.9% of the drainage clamping group.

Wound complications such as hematoma and acute infection must be taken into consideration for long-period drain clamping protocols [20]. Yamada et al. [67] demonstrated that the hemostatic effects are similar between the 1- and 24-h drain clamping methods after TKR, though there were significantly more complications in the 24-h drain clamping method.

CONCLUSION

Tranexamic acid is a synthetic anti-fibrinolytic agent that results in clot stabilization and reduces blood loss. Though the optimal route of administration in TKA remains controversial, there has been growing interest in the use of TXA as intra-articular plus drain clamping. Through this technique, decreased blood loss and transfusion rate has been observed with few complications. More comparative studies are needed to identify the efficacy of intra-articular tranexamic acid plus drain clamping with optimal dose and drain clamping duration.

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