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Research Article

A Comparative Study Determining the Efficacy of Intravenous Versus Topical Tranexamic Acid Administration in Total Knee Arthroplasty

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Received: September 16, 2020; **Published:** October 30, 2020

Abstract

Introduction: Total knee replacements are one of the most common Orthopaedic procedures performed worldwide and the numbers are rising at exponential rates. Blood loss is a significant concern among the population in which it is commonly performed, infrequently necessitating blood transfusion. The use of tranexamic acid (TXA) has been shown to be efficacious in reducing perioperative bleeding as well as subsequent transfusion rates by multiple meta analyses. But the efficacy and safety of one route of administration over the other are yet to be clearly defined.

Methodology: We present a retrospective cohort study evaluating intravenous (IV) versus topical TXA administration among 120 patients undergoing total knee replacements at a single centre using similar implants and surgical techniques.

Results and Discussion: The mean drop in haemoglobin postoperatively was 0.93 g/dL and 0.89 g/dL in the topical and intravenous groups respectively. These were not found to be statistically significant. No difference was found when assessing for average length of stay, transfusion rates, thromboembolic events, infection and mortality.

Several randomized control trials have demonstrated equal efficacy of topical tranexamic acid administration compared to topical when evaluating for blood loss, transfusion rates, and thromboembolic events. Although topical administration may not be able to achieve optimal therapeutic levels in the local tissues - this has not demonstrably translated into clinical findings. the evidence suggests that the use of topical TXA is superior to its IV counterpart in reducing the overall hospital cost per total knee arthroplasty whilst being equally efficacious in reducing the need for blood transfusions.

Conclusion: Our study demonstrates similar outcomes between IV and topical TXA administration with no reported adverse events. Further studies are needed to establish the ideal dosing, delivery method and whether additional therapeutic agents can further help improve outcomes following total knee arthroplasty.

Keywords: *Total Knee Arthroplasty; Total Knee Replacement; Blood Loss; Tranexamic Acid*

Abbreviations

TXA: Tranexamic Acid; TKR: Total Knee Replacement; IV: Intravenous

Introduction

Over 350,000 patients undergo total knee replacements in the United States every year [1]. It is estimated that 12% of adults over the age of 60 years suffer from symptomatic knee osteoarthritis [2]. The number of joint replacements is forecasted to increase exponentially over the next two decades [3,4]. Total knee replacements are associated with intraoperative and postoperative blood loss, necessitating

allogenic blood transfusion in 10-38% of cases [5-7]. Blood loss in these procedures can range between 1450 - 1790 mL. Blood loss following these procedures can be attributed to the surgical trauma that causes a considerable activation of both the coagulation cascade and fibrinolysis, this is further perpetuated by tourniquet release [8,9]. With the increasing numbers of patients undergoing total knee replacements, we can expect an increase in patients who will be at risk for anaemia and blood transfusions along with their associated morbidities and costs.

Multiple meta-analyses have shown that intravenous administration of tranexamic acid (TXA) reduced postoperative bleeding as well as the need for blood transfusion in patients undergoing joint replacements [10-12]. Formal contraindications to the use of IV TXA include a history of thromboembolic or ischemic events such as: pulmonary embolism, deep venous thrombosis, acute myocardial infraction, ischemic cerebrovascular event, or ischemic retinopathy. The use of topical TXA has gained in popularity considering that its level in peripheral blood is significantly lower after topical administration than intravenous [13]. This increases its safety profile by reducing its thromboembolic risk while allowing us to exploit its haemostatic capabilities [13].

The efficacy of topical TXA compared to placebo during total knee replacements has been supported in trials evaluating different routes of administration such as tissue impregnation before knee closure [13], delivery directly into the wound [14], or delivery through a drain [15]. There have been reports of failure to achieve adequate reduction in blood transfusion through topical administration [16]. Whereas a recent meta-analysis has actually demonstrated that topical TXA may be more efficacious than intravenous. Therefore, it remains unclear whether topical administration of TXA is equal, inferior or superior to intravenous administration.

Objective of the Study

The objective of our study was to assess the efficacy and safety of topical TXA compared to IV TXA in patients undergoing primary unilateral total knee replacements with cemented implants using the same surgical technique at a single institution. The postoperative drop in haemoglobin, blood transfusion rates and associated complications were assessed.

Methods

The study is a retrospective cohort study that has been conducted on a total of 120 patients who underwent a total knee arthroplasty between the dates of January 2015 to January 2017 in our hospital center - King Hamad University Hospital, Kingdom of Bahrain.

In the study, patients who had undergone total knee arthroplasty were divided into two groups. 51 patients allocated to the 1g intravenous tranexamic acid administration and 69 patients with 1g topical tranexamic acid diluted in 50 milliliters of saline.

Hemoglobin levels were collected pre-operatively and post-operatively. The 1-week PRBC transfusion incidence were obtained in number of units transfused. Transfusion requirements were less than 8 g/dl or between 8-9g/dl in cardiac patients or having symptoms of anemia. The length of stay of the patients was also been documented. The incidence of thromboembolic events, infection, and mortality was documented during the follow up period of 8 weeks.

All adults above the age of 50 years with symptomatic grade 3 - 4 osteoarthritis admitted to King Hamad University Hospital to undergo a unilateral total knee replacement were included in the study. The exclusion criteria were patients with other forms of arthritis, proven other sources of active significant bleeding, patients with history of hyper coagulopathy (Factor V Leiden, Protein C/S deficiency, Anti thrombin Deficiency, Antiphospholipid syndrome, Lupus anticoagulant), patients with a history of a coronary stent, patients with history of chronic kidney disease, revision procedures and cases with incomplete data set.

Two consultant orthopedic surgeons were responsible for all surgeries done and performed using a standardized technique. All patients received spinal anesthesia. A pneumatic tourniquet was applied and inflated to 150 mm HG above systolic arterial pressure. An

anterior midline incision was utilized followed by a medial parapatellar approach. Two cemented prosthetic designs were used, cruciate retaining and posterior stabilized prosthesis. Autologous bone graft was used to fill the intramedullary cavity before cementing the implants. After insertion of the implant and hardening of the cement, all excess cement debris was removed, and the knee cavity was thoroughly irrigated. In the intravenous tranexamic acid group, the solution was administered 5 minutes before tourniquet release and in topical group, tranexamic acid was allowed to soak around the implant for a total of 3 minutes before tourniquet release. Wound closure was done in layers and ensured proper tracking of the implanted prosthesis. Post operatively, all patients were started on PCA (patient controlled anesthesia) morphine for a total of 24 hours with oral paracetamol. Standard hospital protocol of DVT (deep vein thrombosis) prophylaxis was used in all patients during their inpatient stay. A total of 3 doses of 750mg ceftriaxone was administered to the patient's post operatively for prophylactic antibiotics cover.

Results

From January 2015, a total of 120 patients were included in the study. 69 patients received topical TXA and 51 patients received intravenous TXA. All patients that underwent total knee arthroplasty in our institution were included in the study. The patient population consisted of 45 male and 75 female patients. The patients ages ranged from 51 to 84 years of age with a mean of 64 for the patients in the topical TXA administration group and 62 in the intravenous group. 27 of the 75 patients in the topical TXA group had Diabetes Mellitus (DM) while 30 patients had DM in the intravenous group. There were 34 patients with hypertension in both groups respectively. The average length of stay in the topical TXA group was 4.5 days in comparison to the topical tranexamic acid group which had an average length of stay of 4.7 days (Table 1). The mean pre and post-operative hemoglobin in the topical TXA patients were 13 g/dl and 12.07 g/dl respectively with a mean difference of -0.93 (p-value 0.756). The mean pre and post-operative hemoglobin in the intravenous TXA group were 12.93 g/dl and 12.04 g/dl respectively with a mean difference of -0.89 (p-value of 0.9) (Table 2 and figures 1-3). Comparing the mean difference hemoglobin of both topical and intravenous TXA administration shows no statistical significance between both groups.

Factor	Topical TXA	Intravenous TXA
Number	69	51
Female	43 (62%)	32 (63%)
Male	26 (38%)	19 (37%)
Age, mean (SD)	64.53623 (6.950624)	62.62745 (5.973143)
Length of Stay, mean (SD)	4.594203 (1.950255)	4.784314 (2.211911)
DM -ve	42 (61%)	21 (41%)
DM +ve	27 (39%)	30 (59%)
HTN -ve	35 (51%)	17 (33%)
HTN +ve	34 (49%)	34 (67%)

Table 1: *Group demographics.*

Factor	Topical TXA	IV TXA	P-value
Pre op Hb, mean (SD)	13 (1.5008821)	12.935294 (1.5773172)	0.82
Post op Hb, mean (SD)	12.072464 (1.3378961)	12.041176 (1.7169946)	0.91
Difference, mean (SD)	-0.927 (0.756)	-0.89 (0.912)	0.83

Table 2: *Hemoglobin levels preoperatively versus postoperatively.*

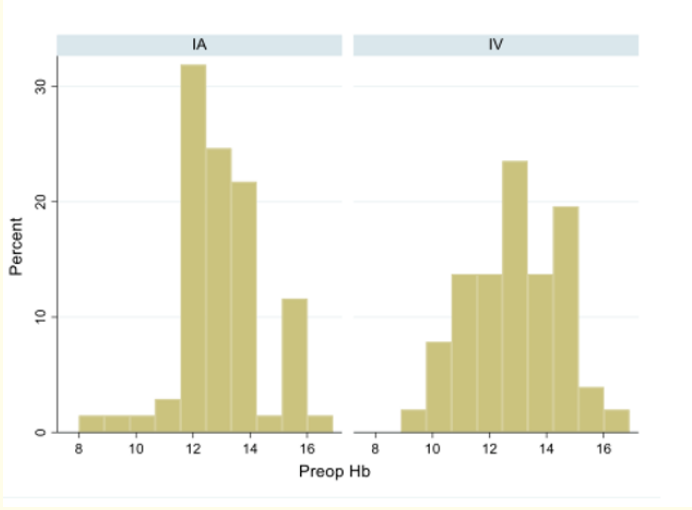

Figure 1: *Preoperative hemoglobin levels among patients in the two groups.*

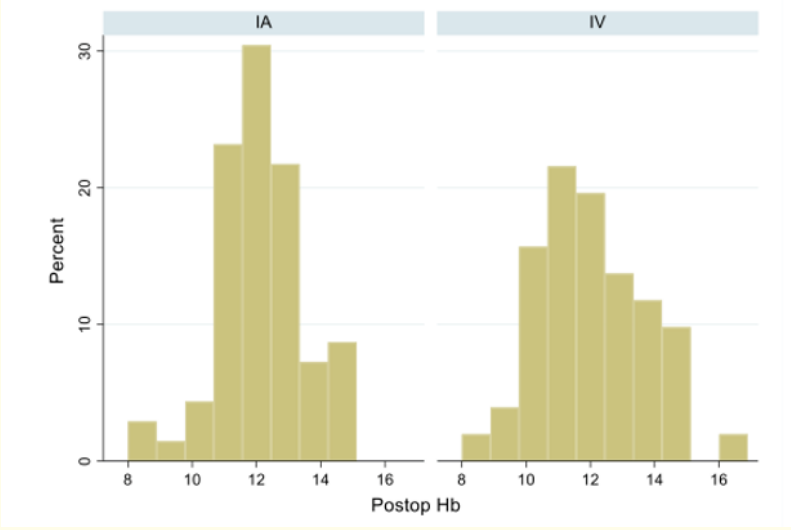

Figure 2: *Postoperative hemoglobin levels among patients in the two groups.*

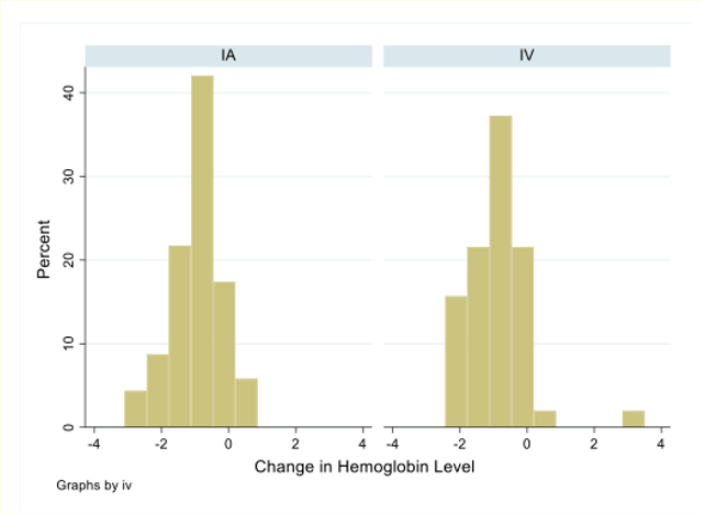

Figure 3: *Postoperative decrease in hemoglobin levels among patients in the two groups.*

Discussion and Conclusion

In our study, we have found no statistical significance between the intravenous and topical tranexamic acid groups when comparing our primary and secondary outcomes. The calculated estimated hemoglobin drops in the topical tranexamic acid group and the intra venous tranexamic acid was 0.927 mg/dl and 0.89 mg/dl with a P-value of 0.83. None of the patients involved in the study received any post-operative blood transfusion. Throughout the follow up period allocated, there was no incidence of thromboembolic events, infection or mortality.

These results are comparable to a meta-analysis conducted by Meena S., *et al*. where a total of 8 randomized clinical trials included 857 patients were analyzed. They concluded that topical TXA has a similar efficacy to IV TXA in reducing total blood loss, transfusion rates and hemoglobin drops without any increase in thromboembolic events [17]. A randomized control study conducted by Tzatzairis TK., *et al*. including 120 patients found similar primary outcomes and they state that there was no statistical significance in the patients' demographics and peri-operative results between both topical and intra venous tranexamic acid groups [18]. Patel JN., *et al*. published a prospective randomized study with 89 patients comparing the topical administration of 2g TXA versus IV administration of 10mg/kg of TXA and measuring primary outcomes similar to our study. They concluded that topical TXA had similar efficacy outcomes when comparing it to Intravenous TXA administration [19].

Wong J., *et al*. conducted a randomized control trial comparing topical TXA with a placebo in total knee arthroplasties. Their study included 99 patients with similar characteristics. They established that topical administration of tranexamic acid reduces post-operative bleeding by 20 - 25% or 300 - 400 ml when compared to placebo [13]. A prospective, double-blind placebo-controlled trial conducted by Georgiadis AG., *et al*. including 101 patients reported a significantly lower post-operative blood loss rate in the TXA group and a significant reduction in the need for blood transfusion when compared to the control group [14]. Other articles published on the local use of tranexamic acid in comparison to placebo concluded that local soaking of tranexamic acid was superior to their placebo counterparts in reducing post-operative blood loss and complication rates [15,16].

Hamlin BR., *et al*. reported a randomized control trial comparing topical TXA to IV TXA in a cohort of 373 patients. This study found that there were higher post-operative transfusion rates in the IV group (2.4%) when compared to the topical TXA (0%) [20]. Another

study supporting topical TXA administration on a total of 150 patients showed that compared to IV TXA, topical administration was more effective in reducing blood loss and transfusion frequency [21]. Huang., *et al*. conducted a prospective randomized control trial between IV 3g and combined topical TXA 1.5g with IV TXA 1.5g to compare the efficacy and safety of each method of administration. A total of 184 patients were included in the study. They concluded that patients in the combined TXA group had a smaller decrease in post-operative haemoglobin, decreased knee pain, decreased blood drainage volume, decreased knee swelling, shorter hospital stays and higher short-term satisfaction when compared to the 3g IV TXA alone [22].

Several meta-analyses have shown that IV administration of TXA is effective in reducing blood loss as well as the need for subsequent blood transfusion [10-12]. Upon IV administration, TXA is widely disseminated through the intravascular and extravascular compartments following which it reaches the synovial fluid by diffusing through the synovial membranes [23,24]. Here its concentration would mirror that in the serum. 90% of TXA would be excreted renally by 24 hours and its half-life in the synovial fluid is approximately 3 hours [23,24]. The therapeutic levels of TXA in the serum is a minimum of 5 - 10 mg/L [25]. The plasma concentration 1 hour after IV administration of low dose TXA (10 mg/kg) has been demonstrated to reach 18 mg/L [23]. In contrast, topical administration of TXA achieves a serum concentration of 4.5 mg/L when a low dose topical regiment (1.5g) is used [13]. Therefore, it is possible that topical administration may fail to achieve therapeutic levels and be clinically inferior to IV administration; albeit no recent clinical trial, systematic review, or meta-analyses so far demonstrates this.

From an economic point of view, it is crucial to monitor the cost of administering TXA and blood products to patients undergoing total knee arthroplasty. A randomized control trial conducted by Alshryda S., *et al*. compared the effects of tranexamic acid in reducing blood loss and hospital costs. They found that the routine use of tranexamic acid reduced the blood transfusion rates by 15.4%, blood loss by 168 ml, length of stay by 1.2 days and reduced the cost per episode by $532 [26]. Chimento GF., *et al*. evaluated similar outcomes to the previous study in a study population of 683 patients undergoing primary TKR utilizing topical TXA. They demonstrated that patient in the TXA group had a higher pharmacy cost in comparison to the placebo group but the average savings of the TXA group when compared to the normal group was around $1500 [27]. Moskal JT., *et al*. compared 3 groups of patients: one group received IV TXA, the second group received topical TXA, and the last group did not receive any TXA. They concluded that the facility cost of patients not receiving any TXA was $84.90/TKR with 0.13 man-hours/TKR. Administering IV TXA patients reduced the cost to $82.59/TKR with a labor cost of 0.007 man-hours/TKR. The most striking finding was that topical TXA resulted in a far greater reduction in facility cost by about $45.76 when compared to no TXA being administered with no employee hours being consumed. None of the patients in this group required blood products [28]. Overall, the evidence suggests that the use of topical TXA is superior to its IV counterpart in reducing the overall hospital cost per total knee arthroplasty whilst being equally efficacious in reducing the need for blood transfusions.

The literature is exhausted with studies demonstrating the efficacy of tranexamic acid in reducing blood loss following total knee arthroplasty. Recent articles have demonstrated equal clinical benefits with topical TXA when compared to IV TXA with an improved safety profile. The related facility cost in utilizing topical TXA is far lower than that with IV TXA, or when TXA is not administered. Our study demonstrates similar outcomes between both the IV and topical TXA groups with no reported adverse events. Further studies are needed to establish the ideal dosing, delivery method, and whether additional therapeutic agents can further help improve outcomes following total knee arthroplasty.

Conflict of Interest

None.

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Volume 11 Issue 11 November 2020