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Research Article

COMPARISON OF EFFICACY OF TRANEXAMIC ACID 10 MG/KG AND 15 MG/KG IN REDUCING BLEEDING AND TRANSFUSIONS IN TOTAL KNEE ARTHROPLASTY

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ABSTRACT

Objective: The objective of this study was to compare the efficacy of tranexamic acid 10 mg/kg and 15 mg/kg in reducing bleeding and transfusions in total knee arthroplasty.

Methods: After approval from the Institutional Ethics Committee, KMC, Mangaluru, 88 patients fulfilling the inclusion criteria of this study undergoing total knee replacements were informed of the study details and consent was obtained for the same. They were randomized into two groups using computer-generated block randomization, i.e., Group A and Group B, and were administered tranexamic acid 10 mg/kg and 15 mg/kg intravenously, respectively. Intraoperatively, hemodynamic parameters were noted. Postoperatively, hemoglobin levels were assessed on days 1 and 3. Transfusions, thromboembolic complications, and duration of hospital stay were noted.

Results: Of the 88 participants of the trial, 44 in Groups A and B each, there were no significant differences in the parameters observed in this study such as intraoperative hemodynamic changes, post-operative fall in hemoglobin on day 3, number of patients requiring transfusions, number of thromboembolic events, and duration of hospital stay. A significant p-value was observed in the fall in hemoglobin in the post-operative day 3 (p=0.043).

Conclusion: About 15 mg/kg tranexamic acid proved to have a lesser fall in hemoglobin on day 3 postoperatively when compared to the 10 mg/kg group. However, the fall of hemoglobin on day 3 was statistically significant and warranted a blood transfusion in two patients in the 10 mg/kg group but did not prolong their hospital stay.

Keywords: Antifibrinolytics, Blood loss, Joint replacements, Blood Product Administration, Hemodynamics.

INTRODUCTION

During the past five decades, total knee arthroplasty (TKA) has been one among the most clinically successful surgeries to be developed. Hence, it has become the most common orthopedic procedure to be performed. Further, considerable growth in numbers of the TKA has been projected in the future [1].

TKA is usually performed on arthritic knees not responding to conservative therapies that include medical, orthotic, and/or rehabilitative methods [2,3]. The aim of conservative therapies is to achieve symptom relief and alteration of disease progression. Unfortunately, they do not offer long-lasting relief [2]. Patient age, severity of osteoarthritis and response to other treatment modalities are considered as the key factors in selecting the patients for total knee arthroplasty [4-6]. The goals of TKA include reducing pain, returning to regular activities of daily living, and achieving a mechanical alignment close to normal [7].

The anesthesia and post-operative care for these patients, often belonging in the geriatric age group, have evolved over time along with the population and techniques of surgery. In the early days, general anesthesia was preferred for these procedures. However, five decades have passed since then, and due to the wider safety margins and better patient outcomes, regional techniques are preferred now [8].

The adverse events and complications include bleeding [9,10], thromboembolic disease, wound complication, vascular injury, readmission, revision, reoperation, and death [1]. Post-operative bleeding and the need for blood transfusions, as a result, have always been a cause of concern among many clinicians. The use of tranexamic acid to counter this has received special attention among patients requiring orthopedic surgery, with numerous studies showing clinical efficacy and cost-effectiveness [11]. Fibrinolysis occurs by surgical trauma, and it is further worsened by the use of a tourniquet which is one of the commonly applied non-pharmacological methods to control bleeding [12-14].

Tranexamic acid is a synthetic analog of lysine, an amino acid, and acts competitively by blocking the lysine binding site of plasminogen. This leads to the inhibition of fibrinolysis [15,16]. There are four methods of administering tranexamic acid to reduce blood loss: Oral, intramuscular, intravenous, and intra-articular. The time taken for maximum plasma levels of tranexamic acid to be reached has been reported to be 30 min for intramuscular, 2 h for oral, and 5–15 min for intravenous administration [17]. The use of tranexamic acid has shown to reduce perioperative blood loss, blood transfusions, and associated costs in major orthopedic surgery [18,19]. Tranexamic acid is usually well-tolerated, gastrointestinal side effects like nausea and diarrhea are the most common adverse events [20], the risk of thromboembolic complications related to tranexamic acid use has been controversial but is present significantly in those with alternative risk factors that include previous thrombotic events and oral hormonal contraceptive use. Seizure activity following tranexamic acid use is very rare [21,22].

However, as many centers seemed to rely on empirical doses such as 1 g or 2 g of tranexamic acid instead of more tailored ones, we tried to compare two regimens of tranexamic acid, i.e. 10 mg/kg and 15 mg/kg in ASA 1 and ASA 2 patients undergoing total knee replacements while we checked for post-operative indicators of bleeding and transfusions in TKA surgeries.

METHODS

This was a prospective, randomized controlled trial done after approval from the Institutional Ethics Committee, in hospitals associated with Kasturba Medical College, Mangalore, from September 2016 to June 2018. 88 ASA Class 1 and 2 patients aged 40–70 years, fulfilling the aforementioned inclusion criteria, posted for elective TKA were chosen using computer-generated block randomization and were divided into two groups: Group A and Group B, i.e., 10 mg/kg and 15 mg/kg, respectively. They also had no known hypersensitivity to tranexamic acid and no history of coagulation disorders. Patients who refused had preoperative hemoglobin <10 mg/dL, and a previous TKA was excluded from the study.

All patients underwent detailed pre-anesthetic evaluation. The study protocol was explained to the patients and written informed consent was obtained. A fasting period of 6 h before the surgery was advised. After shifting the patients to the operating room, monitors such as electrocardiography, non-invasive blood pressure, and SPO2 were connected and the baseline hemodynamics were charted. A peripheral intravenous line was secured and preloaded with 500 ml crystalloids. All the patients were subjected to combined spinal-epidural anesthesia using combined spinal-epidural needle where 2 ml of 0.5% bupivacaine in dextrose solution was given for subarachnoid block and an epidural catheter is guided in and fixed at the point where 5-cm length of the catheter is inside the space. The epidural infusion was activated after 1 h with 0.5% bupivacaine at 5 ml/h until the end of surgery. Tranexamic acid was given in two doses based on their randomly allocated group 20 min before the skin incision and just before tourniquet release. After the completion of the surgery, the patients were shifted to the post-operative room and vitals were monitored. Hemoglobin levels on post-operative day 1 and day 3, perioperative hemodynamic variation, and duration of hospital stay were measured and charted.

Data measurements were done using the formula:

$$n = \frac{2(Z\alpha + Z\beta)^2 \times \sigma^2}{d^2}$$

Where,
n is the sample size
Zα =1.96 at 95% confidence interval
Zβ = 0.84 at 80% power
σ = standard deviation
d =mean

With 95% Confidence Interval, 80% power to ther study.

The data were analyzed using Student's unpaired t-test and Chi-square test. A statistical package SPSS version 17.0 was used to do this analysis and *p<0.05 was considered to be statistically significant.

RESULTS

As shown in Table 1, The study population comprised 88 patients with a mean age of 64.44 years (standard deviation [SD] - 4.966) in Group A and 62.73 in Group B (SD - 4.505) with majority of patients in Group A who were in the age group of 61–65 years (43.18%) and those of Group B who were in the age group of 61–65 (45.45%). These data are statistically not significant with p=0.090

As shown in Table 2, in Group A, 72.73% of patients were female and 27.27% of patients were male. In Group B, 50.09% of patients were female and 40.91% were male. The gender distribution between the two groups was statistically not significant, with p=0.090

As shown in Table 3, all patients belonged to the ASA 2 group.

As exhibited in Table 4, there were no significant differences in the duration of hospital stay in Groups A and B. The difference between the duration of stay between two groups was statistically not significant, p=0.552.

Table 1: Age-wise division of patients

Group	Group A	Group B	Total
Age (years)			
40–55	1 (2.27)	0 (0.00)	18 (1.13)
56–60	7 (15.90)	5 (11.36)	14 (13.63)
61–65	19 (43.18)	20 (45.45)	32 (44.31)
65–70	17 (38.63)	19 (43.18)	36 (40.90)
Total	44 (100.0)	44 (100.0)	88 (100.0)

Table 2: Gender-wise distribution of patients

Group	Group A	Group B	Total
Sex			
Female	32 (72.73)	26 (50.09)	58 (65.90)
Male	12 (27.27)	18 (40.91)	30 (34.09)
Total	44 (100.0)	44 (100.0)	88 (100.0)

Table 3: The ASA status-wise distribution of patients

Group	Group A	Group B	Total
ASA 2	44 (100.0)	44 (100.0)	88 (100.0)

Table 4: Duration of hospital stay

Groups	Group A	Group B
Duration of hospital stay in days		
5	1 (2.27)	2 (4.54)
6	14 (31.81)	22 (50)
7	19 (43.18)	10 (22.72)
8 and above	10 (22.72)	10 (22.72)

Table 5: Transfusion rates of both groups

Groups	Group A	Group B
Transfusion		
No	42 (95.46)	44 (100)
Yes	2 (4.54)	0 (0)

Table 6: Mean hemoglobin on pre-operative day 1 and 3 of the study groups

Groups	Group A	Group B	p
Hemoglobin levels			
Pre-operative	11.88	12.2	0.419
Day 1	10.83	11.43	0.319
Day 3	10.86	10.89	0.043

Table 5 shows that 4.54% of patients in Group A required transfusion of blood as their hemoglobin was <7 g/dL as compared to 0 in Group B. This value was statistically insignificant with p=0.238.

In Group A, mean hemoglobin level preoperatively was 11.58 with a SD of ±1.359, mean hemoglobin on postoperatively day 1 was 10.829 with SD of ±1.7739, mean hemoglobin on post-operative day 3 was 10.86 with SD of±1.218, while Group B showed mean hemoglobin levels of 12.2 with SD±1.187 pre-operatively, mean hemoglobin on post-operative day 1 was 11.427 with SD±0.8167, and mean hemoglobin on post-operative day 3 was 10.89 with SD±1.153.

As shown in Table 6, the fall in hemoglobin on post-operative day 3 was more in Group A when compared to Group B. This was statistically significant p=0.043.

Hemodynamic parameters

There were no significant changes in both groups observed.

Thromboembolic phenomenon

There were no reported cases of thromboembolism in either group.

DISCUSSION

The main indication for TKA is to relieve pain caused by arthritis that is significant and disabling. Bleeding intraoperatively and postoperatively is one of the main concerns in TKA. The loss of blood could range between 800 ml and 1800 ml. Perioperative transfusions increase the cost of the treatment and the risks of infection and allergic reactions. Since the report by Benoni *et al.* [23], different studies have been published on the efficacy of tranexamic acid in reducing perioperative blood loss in total joint arthroplasty.

Our study compared the efficacy of two doses of tranexamic acid, i.e., 10 mg/kg versus 15 mg/kg in reducing bleeding and transfusions in total knee replacement surgeries.

There were no significant differences in the intraoperative hemodynamic changes in the parameters observed such as heart rate, blood pressure, SpO2, and respiratory rate in the participants of both 10 mg/kg and 15 mg/kg group. There were no thromboembolic events in any participant of this study. There were no statistically significant differences in the duration of hospital stay between both groups.

Two patients in the 10 mg/kg group required blood transfusions, as their post-operative day 3 hemoglobin was <7 mg/dL. However, this was deemed statistically significant. Another study by Good *et al.* [24] who conducted a trial with placebo and tranexamic acid 10 mg/kg iv showed that three patients in their study required blood transfusions even though they received tranexamic acid. This is consistent with the 10 mg/kg group in our study. Another study by Cid and Lozano [25] reaffirms with this as two patients in their 10 mg/kg tranexamic acid group received blood transfusions as compared to the placebo group where 7 patients were transfused with blood products.

Our study observed a significant post-operative fall in hemoglobin on day 3 in the 10 mg/kg group when compared to the 15 mg/kg group. A study by Benoni *et al.* [23] showed that a dose of 10 mg/kg of tranexamic acid reduced the number of patients receiving a blood transfusion and the fall in post-operative hemoglobin. Marra *et al.* [26] reported that no significant differences in maximum loss of hemoglobin were observed between the different treatment groups they studied where the intravenous group received 10 mg/kg tranexamic acid. However, their study suggests that a combination of intra-articular and intravenous tranexamic acid had the least fall in hemoglobin. A study by Tanaka *et al.* [27] where tranexamic acid was given once before surgery and once on deflation of the tourniquet reduced bleeding and transfusions. A similar study by Orpen *et al.* [28] where 15 mg/kg of tranexamic acid given at the time of cementing the prosthesis, before deflation of the tourniquet in TKA, showed that a dose of 15 mg/kg given in such a manner effectively reduced bleeding and transfusions. This is concurrent with our findings where 15 mg/kg group showed a reduced fall in hemoglobin on post-operative day 3 and had nil transfusions compared to the 10 mg/kg group.

Ralley *et al.* [29] studied the effect of one 20 mg/kg dose of tranexamic acid given intraoperatively which was effective in reducing the perioperative decrease in hemoglobin and red blood cell transfusion rates in patients undergoing TKA. However, our study showed that 15 mg/kg was an effective dose as we had nil transfusions and reduced post-operative hemoglobin fall in our study group.

Two studies by Lin *et al.* [30] and Maniar *et al.* [31] showed that two doses of 10 mg/kg in TKA were more effective than single doses of the same drug. As our study compared two doses of tranexamic acid administered twice during the surgery, we found that two intravenous doses of 15 mg/kg are better than the 10 mg/kg.

Poeran *et al.* [7] compared four study groups with none, ≤o g, 2 g, and ≥ g of tranexamic acid, and Castro-Menéndeza *et al.* [32] conducted a study with empirical doses of tranexamic acid as high as 2 g and found that 2 g of tranexamic acid iv had the best effectiveness and safety profile. Morrison *et al.* [33] compared 15 mg/kg versus 30 mg/kg intravenous tranexamic acid. While our study did not go higher than 15 mg/kg in terms of dosing, we have found comparable results with the same in terms of rates of transfusion and fall in hemoglobin.

CONCLUSION

There were no significant differences in the intraoperative hemodynamic changes in the parameters observed such as heart rate, blood pressure, SpO2, and respiratory rate in the participants of both 10 mg/kg and 15 mg/kg group. A statistically significant p-value (p=0.043) was observed in the fall in hemoglobin on post-operative day 3 in the 10 mg/kg group as compared to the 15 mg/kg group. Hence, we conclude that 15 mg/kg was more effective than 10 mg/kg in reducing bleeding and transfusions in TKA.

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AUTHORS' CONTRIBUTION

All works pertaining to data collection and analysis were done by the primary author under the guidance of the corresponding author.

CONFLICTS OF INTEREST

The authors have none to declare.

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