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Original Research Article

A randomized comparative study to assess blood loss in patients undergoing total hip arthroplasty with and without the use of tranexamic acid

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Abstract

Background: Total hip arthroplasty could be associated with major intra-operative as well as post-operative blood loss. Post-operative anaemia is a recognized complication which can prolong hospital stay, delay rehabilitation and is poorly tolerated by elderly patients. Blood transfusion carries the risk of infections, anaphylaxis, etc. We examined whether tranexamic acid given before and after total hip arthroplasty reduces intra-operative, post-operative and total operative blood loss and whether the need for post-operative blood transfusion is reduced.
Materials & Methods: A total of 40 patients were included in this study. Group A (n=20, study group) received I.V tranexamic acid (15mg/kg body weight) infusion 10 minutes before incision. 4 hours later, 10mg/kg body weight I.V tranexamic acid was given. Group B (n=20, control group) did not receive any anti fibrinolytic agent. The amount of blood loss, post-operative drop in haemoglobin and the amount of blood transfused was recorded in each case.
Results: Tranexamic acid significantly reduced intra-operative blood loss by 35.68% and total operative blood loss by 22.87% with a 30% reduction in blood transfusion rates compared to the control group. There was no significant effect on post-operative blood loss, duration of surgery or length of hospital stay.
Conclusion: Tranexamic acid when administered perioperatively significantly reduces the operative blood loss in primary total hip arthroplasty surgery with minor side effects. Thus, it can be used effectively in patients undergoing primary total hip arthroplasty to reduce intra-operative blood loss and the need for blood transfusions.

Keywords: Total hip arthroplasty, tranexamic acid, fibrinolysis, haemostatic clots, blood transfusion, anaphylaxis

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Introduction

Total hip arthroplasty is one of the most commonly performed major Orthopaedic surgeries. It has become one of the most successful and cost-effective procedures in recent times since its inception and advancement in the 1960s. Although THA is a relatively safe procedure, it could be associated with major blood loss, both intra- as well as post-operatively, this is an important cause of post-operative morbidity and necessitates blood transfusions, which carries its own spectrum of adverse effects [1].

The femoral intramedullary canal and periacetabular region contain a significant amount of cancellous bone which bleed profusely leading to massive blood loss which is in excess to the soft tissue bleeding making it vulnerable to unrecognized blood loss during and after the surgery [2]. In addition to its adverse physiological impact, bleeding impairs the visibility of the surgical site compromising the precision and success of the procedure. Bleeding can prolong the surgery and necessitate interventions such as blood transfusion and central venous access for the management of hypovolemia.

Increased fibrinolytic activity has been shown to be a major contributing factor for increased blood loss during the surgery. It is estimated blood loss during primary THA can be between 1,000-2,000ml. This could result in a postoperative fall in haemoglobin levels by 3-4g/dl [3].

Studies show that up to 37% of patients undergoing primary THA require blood transfusions [4]. Post-operative anaemia is a recognized complication of total hip arthroplasty which can increase the duration of hospital stay and delay rehabilitation. This could be attributed to the effects of low haemoglobin levels on exercise capacity, endurance and functional status of patients [3, 4]. Higher pre- and post-operative haemoglobin levels are correlated with better and earlier functional recovery, higher patient satisfaction and shorter hospital stay.

Various blood conserving techniques have been adopted to reduce the blood loss intra-operatively as well as post-operatively such as, controlled hypotension, regional anaesthesia, intra-operative blood salvage techniques, autologous blood transfusion, and use of erythropoietin and anti-fibrinolytic agents [5].

Allogenic blood transfusion is the most commonly used remedy, however it carries the risk of infections, immune suppression, anaphylaxis, volume overload, transfusion-related acute lung injury, etc. Transfusion of packed red cells can also cause hypothermia, hyperkalemia and coagulation factor deficiencies, which can lead to coagulopathy, leading to continuous bleeding, renal failure, need for intensive care and even death [6, 7].

As increased fibrinolytic activity has been proven to be a major contributing factor for increased blood loss, a popular approach is to minimize blood loss through the prophylactic use of anti-fibrinolytic agents such as Aprotinin, Tranexamic Acid (TXA) and Epsilon Aminocaproic Acid [8]. Tranexamic acid is a synthetic anti-fibrinolytic agent which counteracts the fibrinolytic process by indirectly blocking the degradation of fibrin and delays the breakdown of haemostatic clots [9].

Studies show a 30% reduction in the need for blood transfusions due to a reduction in blood loss with the use of tranexamic acid in orthopaedic surgeries. The efficiency of tranexamic acid in controlling blood loss has been elaborately studied and various dosing regimens have been suggested, however, there is no fixed dosing till date.

Methodology

A randomized comparative study was conducted from November 2018 to May 2020 involving 40 patients (20 in each group) at a tertiary care hospital in South India.

Inclusion criteria: Patients aged 18 years and above; patients undergoing primary THA for any hip pathology.

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Exclusion criteria: Patients with coagulation disorders or an abnormal coagulation profile (BT; CT; PT; aPTT; low platelet count <1,50,000/ml^3); patients with previous myocardial infarction, pulmonary embolism, deep vein thrombosis, neoplastic disease and hepatic/renal insufficiency; patients who are on long term anti-platelet drugs, known allergy to tranexamic acid.
Written informed consent was obtained from all patients for participating in this study. Institutional ethics committee clearance was obtained. A total of 40 patients were randomized into two equal groups (n=20) using a computer-generated alphabetic sequence by randomization software.

Drug administration: Group A (study group) received a loading dose of tranexamic acid (15 mg/kg body weight) by slow intravenous infusion in 100 ml normal saline, 10 minutes before the surgical incision. After 4 hours of the first dose, 10 mg/kg body weight intravenous tranexamic acid was administered again. Group B (control group) did not receive any anti-fibrinolytic agent.

Position and surgical approach: All patients were operated in the lateral decubitus position and total hip arthroplasty (cemented or uncemented) was done by posterior approach (Southern Moore approach). Combined spinal and epidural anaesthesia was given to all the patients.

Intra-operative blood loss was measured by mop and gauze count with weight difference (post-operative soaked mop and gauze weight minus pre-operative dry mop and gauze weight) using an electronic weighing machine, which was covered with a sterile transparent cover and placed over a sterile OT trolley. Blood collected in the suction apparatus was measured using a measuring beaker after subtracting the amount of normal saline used for irrigation.
Post-operatively, blood loss was measured by the amount of blood collected in the drain (Romovac no. 14) at 48 hours and later drain was removed. Symptoms for deep vein thrombosis and pulmonary embolism were monitored throughout the post-operative period. The decision to transfuse packed red blood cells was made by the treating physician after clinical and laboratory assessment of anaemia. Patients who were having haemoglobin levels less than 10gm% or had clinical symptoms on the second post-operative day were transfused with an appropriate quantity of packed red blood cells.

Prophylaxis: All patients received post-operative deep vein thrombosis prophylaxis (Inj. Enoxaparin 40mg subcutaneously, once a day) from the second post-operative day and physiotherapy in the form of ankle pumps, static and dynamic quadriceps exercises were started.

Statistical methods: Descriptive and inferential statistical analysis was carried out [10-12]. Student t test (two tailed, independent) was used to find the significance of study parameters on continuous scale between two groups on metric parameters. Leven's test was performed to assess the homogeneity of variance. Student t test (two tailed, dependent) was used to find the significance of study parameters on continuous scale within each group. Chi-square/Fisher Exact test was used to find the significance of study parameters on categorical scale between two or more groups, non-parametric setting for qualitative data analysis. Statistical software namely SPSS 22.0 and R environment ver. 3.2.2 were used for the analysis of the data and Microsoft Word and Excel were used to generate graphs and tables.

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Results

Table 1: Duration of surgery among the two groups

Duration (minutes)	Group A	Group B	Total
<100	6(30%)	1(5%)	7(17.5%)
100-150	6(30%)	7(35%)	13(32.5%)
151-200	4(20%)	11(55%)	15(37.5%)
>200	4(20%)	1(5%)	5(12.5%)
Total	20(100%)	20(100%)	40(100%)
Mean ± SD	144.25±61.21	156.25±29.97	150.25±47.95

Duration of surgery among the groups was not statistically significant (p=0.436), with a mean duration of 144.25 in group A and 156.25 in group B.

Table 2: Post-operative haemoglobin drop (comparing pre-operative and post-operative Hb) between the two groups

Variables	Group A	Group B	Total	p value
Pre-op Hb	12.52±1.28	12.46±0.84	12.49±1.09	0.874
Post-op Hb	10.69±1.21	9.74±0.97	10.22±1.18	0.010*
Hb% drop	1.82±1.25	2.73±0.59	2.28±1.07	0.005*

The post-operative mean Hb% drop was more in group B (2.73±0.59gm/dl) than in group A (1.82±1.25gm/dl) which was statistically significant (p=0.005*).

Table 3: Mop weight difference (comparing pre-operative and post-operative mop weight) between the groups

Variables	Group A	Group B	Total	p value
Pre-op total mop weight (gm)	89.05±38.03	82.65±20.71	85.85±30.40	0.513
Post-op total mop weight (gm)	223.70±122.33	290.60±79.01	257.15±107.14	0.047*
Mop weight difference (gm)	134.75±88.99	207.95±66.18	171.35±85.83	0.005*

Post-operative mean mop weight difference was more in group B (207.95±66.18gm) than in group A (134.75±88.99gm) which was statistically significant (p=0.005*).

Table 4: Gauze weight difference (comparing pre-operative and post-operative gauze weight) between the two groups

Variables	Group A	Group B	Total	p value
Pre-op total gauze weight (gm)	69.80±22.58	71.60±11.53	70.70±17.72	0.753
Post-op total gauze weight (gm)	167.50±87.23	170.45±52.55	168.97±71.10	0.898
Gauze weight difference (gm)	97.70±68.12	99.35±44.56	98.52±56.82	0.928

Post-operative mean gauze weight difference was higher in group B (99.35±44.56gm) compared to group A (97.70±68.12gm), however, this difference was not statistically significant (p=0.928).

Table 5: Blood loss comparison between the groups

Variables	Group A	Group B	Total	p value
Suction collection (intra-op bleeding) ml	301.50±222.74	468.00±155.31	384.75±207.34	0.0009*
Drain collection (after 48 hrs) ml	214.50±135.97	214.50±36.63	214.50±98.29	1.000
Total bleeding (intra- and post-op) ml	526.00±308.38	682.50±169.70	604.25±258.14	0.054
Difference at 48 hrs	87.00	253.50	170.25	-
Within group p value	0.061	<0.001*	0.003*	-

The mean suction collection (Intra-operative blood loss) in group A was (301.50 ± 222.74ml) and in group B was (468.00 ± 155.31ml) which was statistically significant (p-0.0009*).

Table 6: Total number of blood transfusions among the two groups

Blood transfusion	Group A	Group B	Total
Nil	16(80%)	10(50%)	26(65%)
Yes	4(20%)	10(50%)	14(35%)
1 pint	3(15%)	6(30%)	9(22.5%)
2 pints	1(5%)	4(20%)	5(12.5%)

The total number of patients requiring post-operative blood transfusion was 14, among which 4 patients (20%) were from group A and 10 patients (50%) were from group B, which is statistically significant (p-0.047*).

Table 7: Side effects of tranexamic acid

Side Effects	Group A (n=20)	Group B (n=20)	Total (n=40)
Nil	16(80%)	18(90%)	34(85%)
Yes	4(20%)	2(10%)	6(15%)
- Nausea	2(10%)	1(5%)	3(7.5%)
- Vomiting	1(5%)	1(5%)	2(5%)
- Headache	1(5%)	0(0%)	1(2.5%)

Discussion

Tranexamic acid inhibits fibrinolysis mainly by blocking the Lysine binding sites of plasminogen, the same sites where plasminogen binds to fibrin. On the surface of fibrin, plasminogen is activated to plasmin and activates the degradation of the fibrin molecules.
A study by Krishnamurti C *et al*., (1994) found that tranexamic acid inhibits clot lysis more efficiently when it was administered before clot formation [13]. For this reason, in our study we used tranexamic acid 10 minutes before the incision. Therapeutic blood concentration of tranexamic acid is 5-10mg/l. Theoretically, to reach this anti-fibrinolytic level during surgery, it should be administered at a dose of 15mg/kg body weight intravenously just before the surgical incision, which results in decreased intra-operative bleeding. However, only few studies have specifically proven that tranexamic acid significantly reduces intra-operative bleeding.
Our study was designed to confirm the beneficial and safety aspects of tranexamic acid given during and after total hip arthroplasty, comparing two groups of patients who underwent elective unilateral total hip arthroplasty. The treatment protocol was standardized and was based on tranexamic acid pharmacokinetics and post-arthroplasty fibrinolysis. Peak serum tranexamic acid levels are reached immediately upon intravenous administration. The elimination half-life of this drug is 3.5-4 hours.

Effect on the duration of surgery: In our study, the mean surgical duration was shorter in the study group patients (144.25±61.21 minutes) compared to control group patients (156.25±29.97 minutes) by 12 minutes, which was not statistically significant (p=0.434). A study done by Wei W *et al*., in 2016 had a mean surgical duration of 103 ± 23 minutes in the control group and 104 ± 22 minutes in the study group, which was not statistically significant (p=0.583) [14], which correlates with our study.

Haemoglobin drop: It was noted in our study that the mean pre-operative Hb in the study group (12.52±1.28 mg/dl) was comparable with that of the control group (12.46±0.84 mg/dl),

but the mean post-operative Hb% drop was higher in the control group (2.73±0.59 mg/dl) compared to that of the study group (1.82±1.25 mg/dl) by a difference of 0.91 mg/dl which was statistically significant (p=0.005). Similar results were obtained in a study done by Xie J *et al*., in 2015 where the mean post-operative Hb% drop in the study group (3.36±0.78 mg/dl) was less compared to that of the control group (3.89±0.72 mg/dl) and it was statistically significant (p<0.001) [15]. Another study done by Harry A Demos *et al*., in 2017 had found similar results with respect to mean post-operative Hb% drop, where study group (2.73mg/dl) had less Hb% drop compared to control group (3.39 mg/dl) by difference of 0.66mg/dl, which was statistically significant. (p=0.001)

Intra- and post-operative bleeding: We found that the intra-operative bleeding was more in the control group (468.00±155.31ml) than the study group (301.50±222.74ml) and further it was noted that tranexamic acid reduced intra-operative blood loss by 35.68% in study group compared to control group, which was statistically significant (p=0.0009).

With respect to post-operative bleeding (drain collection at 48 hours), we could not find a significant difference between the two groups (p=1.00), but when total blood loss (intra- and post-operative) was taken into account, it was found that the control group (682.50±169.70 ml) had more bleeding than the study group (526.00±308.38 ml) by 22.87% which is statistically near significant (p=0.054).

In a study conducted by Yamasaki *et al*., in 2005, it was found that there was not much difference with respect to intra-operative blood loss between the study group (607±298ml) and the control group (633±220 ml), however the cumulative blood loss at each post-operative interval in the study group was significantly lower than that in the control group (p<0.001) and the total blood loss in the study group (1349±478 ml) was significantly lower than that in the control group (1646±469 ml) (p<0.01) [16].

Our study has shown that the intra-operative blood loss and total blood loss were reduced significantly in the tranexamic acid group. This was not consistent with the findings of the above study. The decreased intra-operative blood loss in the study group could be because of the inhibition of early fibrinolysis before the body's usual response which is seen after 24 hours.

In our study, there was no significant difference with respect to post-operative blood loss between the two groups and did not correlate with the aforementioned study. This could be because fibrinolysis activation is a cascade process that is most easily inhibited in its early phase. TXA mainly inhibits clot lysis more efficiently when administered before clot formation than after the fibrin clot has formed. Once plasminogen is bound to the fibrin surface, TXA will no longer be effective. This could be the reason why tranexamic acid has minimal effect when given at the end of surgery.

Blood transfusion: Considering the amount of total blood loss and Hb% drop, in our study, post-operative blood transfusions were more in the control group (10 patients) than in the study group (4 patients) by 30%, which was statistically significant (p=0.047) and the number of blood units transfused per patient was also higher in control group (4 patients received 2 pints each) than study group and none of the patients in our study were transfused intra-operatively.

Similar results were seen in a study conducted by Husted *et al*., in 2003 with 20 patients in each group, post-operative blood transfusions were more in the control group (7 patients) than in the study group (2 patients) by 25%, which was statistically significant (p=0.034) which correlates with our study [17].

Another study done by Hsu CH *et al*., in 2015, with 30 patients in each group, post-operative blood transfusions were more in the control group (9 patients) than in the study group (2 patients) by 23.3%, which was statistically significant (p=0.021) [18].

Side effects: We observed negligible side effects in 15% of the patients including both the groups (4 patients in group A and 2 patients in group B) among which nausea (7.5%) was the predominant side effect, vomiting (5%) and headache (2.5%). All three were found to be the common side effects in most major orthopaedic surgeries and most of these side effects were also observed in other similar studies.

Complications: Both groups of patients had an equal incidence (10%) of late post-operative minimal surgical wound gaping, which was managed with regular saline dressings. None of our patients had serious complications such as DVT, myocardial infarction, pulmonary embolism, deep surgical site infections, etc.

Length of hospital stay: There was no significant difference in the total duration of hospital stay between the groups, considering from the day of surgery to the day of discharge, with mean duration of stay in the study group was 12.05±3.03 days and in the control group was 11.35±1.59 days, which was not statistically significant (p=0.367). One patient in study group who had a surgical complication of posterior hip dislocation stayed for 22 days post-operatively. A study done by Yi Z *et al*., in 2016, also showed no significant difference in the length of hospital stay among the two groups [19], which is consistent with our study.

Limitations of our study: We did not evaluate the blood loss separately in cemented and uncemented total hip arthroplasty. In our study, both the operating surgeon and the anaesthetist were not blinded to the randomization. We did not calculate the blood loss due to spillage over drapes and gowns of the surgeons and the operating room floor.

Conclusion

In conclusion, our randomized clinical study has shown that patients undergoing primary total hip arthroplasty, when administered tranexamic acid of standardized intravenous infusion of 15mg/kg body weight, 10 minutes before the incision and 10mg/kg body weight 4 hours after the first dose, was a simple, safe and effective way of reducing intra-operative and total operative blood loss with the maintenance of a higher post-operative haemoglobin levels and thereby reducing the need for blood transfusions and eliminating the likely risks of transfusion.

However, we could not find much benefit with tranexamic acid usage in reducing post-operative blood loss and decreasing the total duration hospital stay. The above mentioned dosage seems to be adequate to maintain fibrinolytic inhibition in the early hyper-fibrinolytic stage and prevent the post-operative fibrinolytic shutdown. The treatment appeared to be safe with minimal side effects. Further large-scale randomized trials are required to ascertain the most effective dose and limitations of tranexamic acid.

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