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Prospective Randomized Study of the Combined Effect of Tranexamic Acid and Tourniquet on Blood Loss in Total Knee Replacement

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Abstract

Background: Tranexamic acid is widely used to limit blood loss after Total Knee Replacement as has been proved by numerous studies. There are many studies in literature which have assessed the blood loss after knee replacement with and without the use of tourniquet, and with and without the use of tranexamic acid separately in the postoperative period. In our hospital, Knee replacements are being done only after application of tourniquet. This is the first study which has randomised patients into four groups and compared the difference in blood loss between immediate and delayed release of tourniquet with and without Tranexamic acid. Patients were assessed by the parameters of postoperative drain volume and haemoglobin levels at 48hours in all four groups. There was a significant statistical advantage to the patient in terms of reduced blood loss and need for postoperative blood transfusion in Group D patients compared to A and B. This significantly reduces morbidity, especially in cases who would significantly benefit while undergoing bilateral knee replacements in the same sitting under a single anaesthesia.

Materials and methods: (The use of tourniquet limits blood loss during surgery, however it activates the fibrinolytic process. This causes more blood loss after surgery. Tranexamic acid, by virtue of its chemical properties, reduces postoperative blood loss. Delayed release of tourniquet also has the same effect to some extent. These factors and their effect on postoperative blood loss have been studied separately, but there is no study which combines these factors). In this prospective study, 60 consecutive patients undergoing primary TKR for primary osteoarthritis of Knee were operated under spinal anaesthesia, tourniquet was applied, and a suction drain inserted during closure in every case. Tourniquet was not released before closure, but only after closure and compression dressing was applied. (The factors of present time of release of drain, and the use of tranexamic acid postoperatively were randomised into groups as follows-

The study population was allocated into 4 groups using closed envelope technique for randomization:

Group 'A'- Immediate drain release after wound closure and release of tourniquet and no Tranexamic acid.

Group 'B'- Delayed drain release (after one hour of wound closure and release of tourniquet) and no Tranexamic acid.

Group 'C'-Immediate drain release and 10mg/kg Tranexamic acid was administered intravenously in immediate post-operative period.

Group 'D' -Delayed drain release (after one hour of wound closure and release of tourniquet) and 10 mg/kg.

Tranexamic acid was administered intravenously. The four groups were formed to evaluate extent of blood loss postoperatively to rationalise a protocol regarding timing of tourniquet release combined with the use of Intravenous Tranexamic acid which would significantly reduce blood loss after surgery as it is common to do bilateral knee replacements in the same sitting under a single anaesthesia. The study aimed to identify in which group of patient's blood loss is minimal so that it could be universally applied to all cases to the benefit of patients. Postoperative volume of blood loss and haemoglobin levels were used to assess the effectiveness of the four protocols used.

Results: On comparison of group A with group D in terms of decrease in post-operative haemoglobin, p value was found highly significant and was 0.000. On comparison of group A with group C and D in terms of volume of drain, p value was found to be highly significant and was 0.001 and 0.000 respectively. On comparison of group B with group D in terms of drain volume, p value was found to be highly significant i.e. 0.000.

Conclusion: We found that delayed release of drain after one hour of wound closure and release of tourniquet postoperatively along with injection of tranexamic acid postoperatively in TKR significantly reduces blood loss and requirement of blood transfusion postoperatively.

Keywords: Blood loss; Delayed release; Tourniquet; Total knee replacement; Tranexamic acid

Introduction

Major blood loss, defined as a loss of 20% of total blood volume or more is associated with major orthopaedic procedures including hip and knee replacement and spine surgery [1], and increased blood loss often results in anaemia requiring blood transfusion. Total knee arthroplasty is associated with major post-operative blood loss of approximately 800 to 1200 ml [1] and this blood loss can be measured in the suction drain. This drainage volume, however, does not reflect the entire loss of red cells. A hidden loss of more than 700 ml, probably from haematoma formation also occurs [2]. Application of a tourniquet offers better visualisation of structures during surgery, with better cementing, reduced operative time and decreased rates of infection. Prolonged tourniquet use may cause blisters on the skin, hematoma, increased oozing depending on degree of soft tissue release and cuts and muscle injury, decreased postoperative range of motion and increased incidence of thrombosis [3]. haematoma contributes to hidden blood loss not measurable in the drain volume.

Many methods have been tried to reduce wound drainage following TKA including surgical haemostasis following release of tourniquet, the use of fibrin tissue adhesive, instilling epinephrine into joint post-operatively, and intravenous administration of tranexamic acid [4]. Surgery-induced tissue trauma activates the fibrinolytic system by releasing tissue plasminogen activator (t-PA) which converts plasminogen to plasmin, leading to increased blood loss in the postoperative period. Hiippla ST, et al. [5] concluded that the application of a pneumatic tourniquet in orthopaedic procedures enhances local fibrinolysis and Total Knee Replacement (TKR) is often carried out using a tourniquet to minimize intraoperative blood loss. Blood transfusion involves the risk of transmission of viral diseases such as the human immunodeficiency virus, hepatitis, and cytomegalovirus, as well as transfusion reaction. Hence, there has been a constant search for safer methods of reducing blood loss in orthopaedic surgery and a more rational approach would be to enhance haemostasis and sealing of vessels at the site of the operation to achieve this goal [2].

Tranexamic acid, a synthetic derivative of the amino acid lysine, is an effective antifibrinolytic agent. It acts by reversibly blocking lysine binding sites on the plasminogen molecules and inhibiting plasmin formation. Tranexamic acid is being increasingly used in orthopaedic surgery due to its efficacy, safety and low cost. Several studies that have shown the efficacy of tranexamic acid in TKR [6]. (Various studies have been done on the application of tourniquet in TKR, and many surgeons believe that its application increases postoperative blood loss. However, the ease of performing the procedure after its application makes it a universally more accepted protocol for most surgeons. The study aims to find a method where tourniquet can be used without excessive postoperative blood loss by either delaying release of the drain or combining it with Tranexamic acid injection or both). There is no study in literature available at present which evaluates the combined effect of a tourniquet along with Tranexamic acid in total knee replacement, hence these 4 groups were formed, and this study was done. Our study is to evaluate the effect of delayed release of drain with or without tranexamic acid on blood loss in total knee replacement.

Materials and methods

The study was conducted between June 2012 to July 2013 at the Department of Orthopaedics, Northern Railway Central Hospital, New Delhi. After clearance from ethical committee, a well written informed consent was taken.

Inclusion Criteria

Patients undergoing primary TKR at our institution.

Exclusion Criteria

1) Known allergy to tranexamic acid. - Known allergy was elicited mainly through history. No transdermal testing was done in any patient. Patients were asked for past history of use-especially in female patients for menstrual bleeding, history of difficulty in breathing or vision after its use, joint and muscle pain, skin rashes etc.
2) Revision TKR.
3) History of bleeding diathesis / blood dyscrasias.
4) History of haemoglobinopathies. This was elicited through Family history, area of residence (eg-some tribes of Madhya Pradesh are more prone to sickle cell anaemia)., history of prolonged bleeding after injury, frequent nose bleeds, anaemia etc. Routine haematological testing for haemoglobinopathy was not done in this study (unless patient had a suggestive history).
5) Previous history of thrombosis.
6) Secondary Osteoarthritis

In this prospective study, 60consecutive patients undergoing primary TKR were taken. 60 patients were chosen according to the number of knee replacements done in our hospital in one year. As this is heavily dependent on availability of implant, a reasonable number of 60 was chosen, even though the overall sample size per group is small. All patients were operated under spinal anaesthesia, tourniquet was applied, and suction drain inserted during closure. Injection ceftriaxone 1gm intravenous was given 2 hours prior to incision; 6 hours post-operative; and then at 8 hourly intervals till 24 hours post-operatively, followed by oral cefuroxime axetil

500 mg 12 hours for 10 days. Post-operatively haemoglobin level was checked after 48 hours. Volume of drain was measured after 48 hours of surgery. Stitch removal was done on the 10thpost-operativeday (day 1 is day of surgery) unless there was some wound complication.

The study population was allocated into 4 groups using the closed envelope technique for randomization. There were three operating surgeons in the department. Sealed box with20 slips marked A, B, C and D each were put into the box. After consent of patient, a slip was picked by the operating surgeon from the box which had 60 slips at the start of the study, and the box was sealed before the study was started.

1) Group 'A'- The drain was released immediately after deflating the tourniquet and no tranexamic acid was administered.
2) Group 'B'-The drain was released one hour after deflating the tourniquet and no tranexamic acid was administered.
3) Group 'C'- The drain was released immediately after deflating the tourniquet and 10mg/kg Tranexamic acid was administered intravenously in immediate post-operative period.
4) Group 'D'-The drain was released one hour after deflating the tourniquet and 10mg/kg Tranexamic acid was administered intravenously in the immediate postoperative period.
5) The criteria used for evaluation of patients were -
6) Preoperative haemoglobin level-No patient was taken for surgery unless pre-operative haemoglobin >10 gm%
7) Postoperative haemoglobin level
8) Volume of drain (ml)
9) Units of whole blood transfused -Blood transfusion was given if Postoperative haemoglobin was less than 10 gm% after 48 hours of surgery.
10) Duration of hospital Stay-Normal duration was 10 days, with Day 1 being counted as day of surgery.

Statistical Analysis

Statistical analysis was conducted with Statistical Package for the Social Sciences (SPSS) statistical software version 15.0 and Microsoft excel by using Chi-Square test, Paired and unpaired student's t test. The results were expressed as Mean ± SD. $P < 0.05$ was regarded as statistically significant, $P < 0.001$ was taken as highly significant, and $P > 0.05$ was regarded as non-significant.

1) On comparison of group A with group D in terms of decrease in haemoglobin, p value was found highly significant was 0.000.
2) On comparison of group A with group C and D in terms of volume of drain, p value was found to be highly significant was 0.001 and 0.000 respectively.
3) On comparison of group B with group D in terms of drain volume, p value was found to be highly significant was 0.000

Results

Female	13	8	11	11	43
	86.7%	53.3%	73.3%	73.3%	71.7%
Male	2	7	4	4	17
	13.3%	46.7%	26.7%	26.7%	28.3%
Total	15	15	15	15	60
	100.0%	100.0%	100.0%	100.0%	100.0%

Table 1: Sex distribution.

Age (in					
< 50	0	0	2	1	3
	.0%	.0%	13.3%	6.7%	5.0%
50 - 60	5	4	2	5	16
	33.3%	26.7%	13.3%	33.3%	26.7%
60 - 70	6	5	3	3	17
	40.0%	33.3%	20.0%	20.0%	28.3%
70 - 80	4	4	7	5	20
	26.7%	26.7%	46.7%	33.3%	33.3%
>= 80	0	2	1	1	4
	.0%	13.3%	6.7%	6.7%	6.7%
Total	15	15	15	15	60
	100.0%	100.0%	100.0%	100.0%	100.0%

Table 2: Age distribution.

Descriptives

Weight (kg)	A	15	70.87	9.797	
	B	15	75.20	7.618	
	C	15	73.73	12.714	.214
	D	15	76.47	8.831	
	Total	60	74.07	9.891	
Height (metres)	A	15	1.5260	.05578	
	B	15	1.5793	.05496	
	C	15	1.5620	.06774	.183
	D	15	1.5547	.07918	
	Total	60	1.5555	.06639	
Body Mass Index	A	15	30.5057	3.96783	
	B	15	30.3034	3.27965	
	C	15	30.4836	6.34724	.451
	D	15	31.7047	3.07175	
	Total	60	30.7493	4.28980	

Table 3: Height, weight and BMI.

Descriptives

Preop Hb	A	15	12.1467	1.02181	
	B	15	12.2867	1.40858	
	C	15	12.1067	1.31555	.167
	D	15	11.3800	.96006	
	Total	60	11.9800	1.21429	
Postop Hb	A	15	10.0333	.97370	
	B	15	10.6667	1.26020	
	C	15	10.7267	1.28534	.302
	D	15	10.3800	.81258	
	Total	60	10.4517	1.10783	
Decrease in Hb	A	15	2.1133	.58781	
	B	15	1.6200	.75612	
	C	15	1.3800	.61899	.001
	D	15	1.0000	.57941	
	Total	60	1.5283	.74426	
% decrease in Hb	A	15	17.3719	4.38438	
	B	15	13.0575	5.58995	
	C	15	11.3464	4.96126	.001
	D	15	8.6169	4.76214	
	Total	60	12.5982	5.78560	

Table 4: Comparison of Pre-op and Post-op Haemoglobin.

Multiple Comparisons

Volume of Drain (ml)	A	B	.022
		C	.001
		D	.000
	B	A	.022
		C	1.000
		D	.000
	C	A	.001
		B	1.000
		D	.001
	D	A	.000
		B	.000
		C	.001

Table 5: Volume of drain and hospital stay.

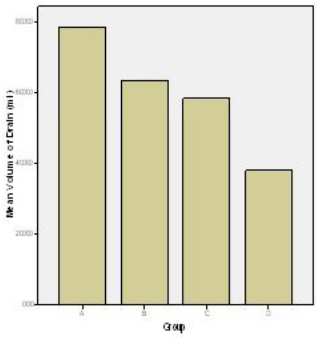
Descriptives

Volume of Drain (ml)	A	15	783.3333	126.74027	
	B	15	631.6667	157.96323	
	C	15	583.3333	154.88091	.000
	D	15	378.3333	100.38616	
	Total	60	594.1667	197.84896	
Hospital Stay (days)	A	15	16.6667	2.58199	
	B	15	16.5333	2.61498	
	C	15	17.3333	2.87021	.376
	D	15	15.7333	1.66762	
	Total	60	16.5667	2.47952	

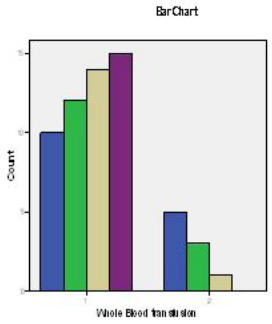
Table 6: Whole blood transfusion.

Whole Blood					
1	10	12	14	15	51
	66.7%	80.0%	93.3%	100.0%	85.0%
2	5	3	1	0	9
	33.3%	20.0%	6.7%	.0%	15.0%
Total	15	15	15	15	60
	100.0%	100.0%	100.0%	100.0%	100.0%

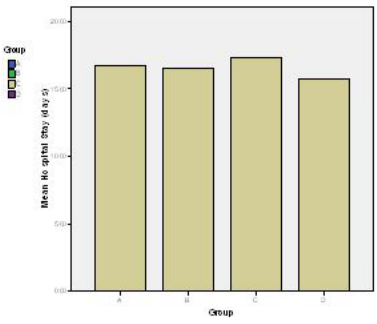
1) Females dominated our study (71.7%).
2) Mean age of patients in group A was 63.06 year, in group B was 67.4 year, in group C was 65.46 year and in group D was 64.93 year.
3) Mean preoperative haemoglobin in group A was 12.14 gm/dl, in group B was 12.28 gm/dl, in group C was 12.10 gm/dl, in group D was 11.38 gm/dl (Table 1).
4) Mean postoperative haemoglobin in group A was 10.033 gm/dl, in group B was 10.667gm/dl, in group C was 10.72gm/dl and in group D was 10.38 gm/dl (Table 1).
5) Decrease in haemoglobin in group A was 2.11 gm/dl, in group B was 1.62 gm/dl, in group C was 1.38gm/dl and in group D was 1.000 gm/dl.
6) Mean volume of drain in group A was 733.33 ml, in group B was 631.67 ml, in group C was 583.33 ml and in group D was 378.33 ml. (Table and bar Graph 1).
7) Mean hospital stay in group A was 16.67 day, in group B was 16.53 day, in group C was 17.33 day and in group D was 15.73 day. (Table and bar Graph 2).
8) No. of units of whole blood transfusion in group A was 20, in group B was 18, in group C was 16 and in group D was 15. (Table and bar Graph 3).



Graph 1



Graph 2



Graph 3

Discussion

The reported blood loss associated with TKA ranges from 600 ml to 1550 ml depending on the clinical setting and study designs. The different methods used to define and determine perioperative blood loss are probably the main reason for this great variation. At best, carefully performed measurements are an acceptable estimate of the true blood loss. However, the figures represented in many investigations are based on the estimate retrieved from patient records retrospectively. Benani G and Fredin H [7] did a randomised, double-blind study on 86 patients and investigated the effect, Tranexamic acid on blood loss and blood transfusion in knee arthroplasty. They concluded that Tranexamic acid should be given prophylactically in order to be effective. The present study was undertaken to detect the effect of delayed release of drain with or without tranexamic acid on blood loss in TKA. We compared all the 4 groups on the basis of pre-operative and post-operative haemoglobin, drainage volume, units of whole blood transfused, no. of dressing changed or reinforcements in the first 48 hours and duration of hospital stay.

Review of literature search does not contain a single study in which all these 4 groups are compared.

N Roy et all found that average amount of postoperative drainage in immediate release group was 1050 ml compared to 732 ml in the delayed release group which was statistically significant p value < 0.001, The corrected drop in haemoglobin level at 48 hours in the delayed release group was 0.17 gm. less than in the immediate release group, although this was not statistically significant. The total no. of units transfused in group A was 78 units compared to 66 units in the group B. There were no statistical significant differences between lengths of the stay [4].

In our study in group A drainage was 783.33 ml compared to 631.66 ml in the group B that was statistically significant p value was 0.022, the corrected drop in haemoglobin level at 48 hours in group B was 0.49 gm less than group B although it was not statistically significant, the total no. of blood transfused in group A was 20 units in 15 patients as compared to 18 units in group B, there were no. statistical significant differences between length of the stay, bruising around the knee. Our study has nearly similar results to N ROY's study on comparison of group A and group B. Chareancholvanich K, et al. in their study found the blood loss in group C was 724±246 and in group D was 526±222 and decrease in haemoglobin in group C at 12 hours was 0.9-3.8 and in group D was 0.4-3.6. [8] in our study blood loss in group C was 583.33±154.88 and in group D was 378.33±100.38 and decrease in haemoglobin at 48 hours in group C was 1.38±0.62 and in group D was 1.00±0.58.our results seem to be better than this study.

In our study volume of drain in:

Group A was 783.33 ±126.74 ml.

Group B was 631.67 ±157.96 ml.

Group C was 583.33 ±154.88 ml.

Group D was 378.33 ±100.38 ml.

On comparison of group A with group B in terms of volume of drain p value is 0.022 that is statistically significant, on comparison of group A with group C p value is 0.001 that is highly significant, on comparison of group A with group D p value was 0.000 that is also highly significant. On comparison of group B with group C p value was 1.000 that is statistically not significant and on comparison of group B with group D, p value was 0.000 that is highly significant. On comparison of group C with group D p value was 0.001 that is statistically highly significant. So, in terms of blood loss in patients with tranexamic acid with delay release of drain has less amount of blood loss than all the other groups and has statistically significant values.

In our study decrease in haemoglobin in

Group A was 2.11 ±0.58

Group B was 1.62 ±0.75

Group C was 1.38 ±0.61

Group D was 1.00 ±0.57

On comparison of group A with group B in term of decrease in haemoglobin p value was 0.235 that is statistically not significant, on comparison of group A with group C p value was 0.016 that is statistically significant, on comparison of group A with group D p value was 0.000 that is highly significant, on comparison of group B with group C p value was 1.00 that is not significant, on comparison of group B with group D p value was 0.062 that is also not significant, on comparison of group C with group D p value was 0.656 that is also not statistically significant. So, in term of decrease in the haemoglobin patients with tranexamic acid with delayed release of drain had less amount of blood loss than all other groups and has a statistically significant value.

Holt BT, et al. [9] did a study of 136 primary TKA where patients were randomized for the use of closed-suction, non-rein usable wound drains and concluded that a simple wound drain effectively minimizes the undesirable accumulation of blood in the surrounding soft tissues and the postoperative wound dressing after total knee arthroplasty. In our study we did 19 dressing (11 patients, only one dressing and 4 patients two times dressing) in first 48 hour in group A, 17 dressing (13 patients only one dressing and 2 patients two times dressing) in group B, 17 dressing (13 patients only one dressing and two patients two times dressing) in group C and 16 dressing (14 patients only one times dressing and one patient one dressing) in group D.

In our study number of blood units transfused was 20 (10 patients one-unit transfusion and 5 patients two unit's transfusion) in group A, 18 (12 patients one unit's transfusion and 3 patients two unit's transfusion) in group B, 16 (14 patients one unit's transfusion and 1 patient one-unit transfusion) in group C, 15 unit's transfusion (all 15 patients only one-unit transfusion) in group D.

In our study bruises within 5 cm of incision line and other complication was present in:

8 patients in group A

6 patients in group B

3 patients in group C

3 patients in group D

Overall average hospital stay in our study was 16.566±2.48 day.

In our study, patients with tranexamic acid and delayed release of drain have less volume of drain, less decrease in haemoglobin, less units of blood transfusion required, less hospital stay and less complication than other group. Alshrydas [10] conducted a systematic review and meta-analysis of randomised controlled trials evaluating the effect of Tranexamic Acid (TA) upon blood loss and transfusion in primary total knee replacement. The review used the generic evaluation tool designed by the Cochrane bone, joint and muscle trauma group. A total of 19 trials were eligible: 18 used intravenous administration one also evaluated oral dosing and one trial evaluated topical use. TA showed a plausible consistent reduction in blood transfusion requirements (RR) 5.33; CI 2.44 to 11.65, $p < 0.001$; $I(2) = 0\%$, a finding that should be confirmed by a further well-designed trial. The current evidence from trials does not support an increased risk of deep vein thrombosis (13 trials, 801 patients) or pulmonary embolism (18 trials, 971 patients) due to TA administration.

We therefore conclude that delayed release of drain with tranexamic acid has less post-surgery volume of drain, less hospital stays, less mean decrease in haemoglobin, less amount of blood units required and less dressing changes compared to other groups. Hence, delayed release of drain combined with tranexamic acid in TKR is the best way to decrease volume of postoperative blood loss and decrease morbidity in terms of transfusion requirements and reduced haemoglobin levels. Sample size is small with confounding factors of differing surgical skills (Inter -surgeon variability), varying degrees of soft tissue release which also affect postoperative blood loss. A larger sample size with a single operating surgeon should be done to authenticate a more reliable and universally acceptable protocol, as reduced blood loss will improve postoperative recovery, especially in patients undergoing bilateral Total Knee Replacement in a single sitting under the same anaesthesia.

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