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ORIGINAL ARTICLE

EFFECT OF TRANEXAMIC ACID IN CONTROL OF PERIOPERATIVE BLOOD LOSS ASSOCIATE WITH TOTAL KNEE REPLACEMENT OUR EXPERIENCE

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ABSTRACT: BACKGROUND: Costs of allogenic blood transfusions and the associated risks mandate strategies to reduce blood loss in surgery. The objective of this study was to assess the efficacy of antifibrinolytic treatment in reducing perioperative blood loss during total knee replacement. **MATERIALS AND METHODS:** A prospective study was carried out on 148patients undergoing total knee replacement. 88pts received tranexamic acid 10 mg kg^{-1} i.v. just before the cementation, 3hours post op and 6 hrs later.60 patients did not receive tranexamic acid. External perioperative blood loss was measured by post op amount of drain, and Hb levels and Hematocrit. The number of patients transfused and number of packed red cell (PRC) units transfused was recorded and possible postoperative thrombo embolic complications were studied clinically. **RESULTS:** Amongst 78 pts who were given Cyclokapron, only 10(12.8%) were given blood transfusions and the average transfusions were 3.9 units and Amongst 70 pts who were not given Cyclokapron, 20(28.5%) were given blood transfusions and the average transfusions were 8.7 units. The average blood loss in the group of patients who were given cyclokapron was 1004ml while in the groups which were not given the average blood loss was 1507ml. Clinical assessment did not reveal any thromboembolic complications. **CONCLUSIONS:** Antifibrinolytic agents produce a significant decrease in blood loss in patients undergoing total knee replacement, reflected in a reduction in the number of blood transfusions required. Based on this study we can conclude that three doses of IV tranexamic acid of 10mg/kg, can be used in TKR procedures with proven effectiveness and efficiency to decrease postoperative blood loss in patients undergoing TKR.

KEYWORDS: Tranexamic acid, Bloodloss, Hematocrit, Blood transfusions.

INTRODUCTION: Current surgical technique in total knee arthroplasty (TKA) usually includes the use of tourniquet, resulting in unapparent intraoperative bleeding but substantial postoperative blood loss. Postoperative drainage ranges 500 to 1000 cc, with additional hidden blood loss up to 700 cc.[1] Therefore, total blood loss is calculated, based on pre and postoperative hematocrit values, within a range of 1500 to 1900 cc.[2] Blood loss in TKA patients is multifactorial.

Allogenic blood transfusion associates the currently increased risk of infectious disease transmission. Some of these cannot be detected by the laboratory (Chagas disease, Lyme disease, malaria, prion-mediated diseases), while others support a quantified risk, ranging from VHC (0.8/million), HIV (0.14/million), VHB (1.66/million), to bacterial contamination (2/million).[3] Besides, iatrogenic severe error due to ABO discrepancy is also a potential risk.

The mentioned risks, including incrased morbidity and longer Hospital stays, but also refusals due to religious beliefs (as in the case of Jehovah's witnesses[4]) justify clinical strategies to minimize exposure to allogenic blood transfusion. As hyperfibrinolysis is considered the major cause of

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postoperative bleeding after TKA surgery,[5] antifibronolytic drugs have been proposed, including aprotin, aminocaproic acid, and tranexamic acid. Aprotin, derived from bovine lung, inhibits the serinprotease at the last stage of fibrinolysis, but allergies, thrombosis, nephrotoxicity, and spongiform encephalopathy[6] lead this drug out of the market. Aminocaproic acid is less effective, more expensive and less supported by the literature than tranexamic acid.[7] Tranexamic acid (TXA) is a synthetic analog of serin that reversibly inhibits fibrinolysis by blocking lysine union sites in the plasmin and plasminogen activator molecules. It has been used since more than 20 years in cardiac surgery, urology, gynecology, liver transplants, Orthopaedic surgery etc.

In this context, the aim of our study was to compare transfusion rate, postoperative bleeding, and additional costs, in a consecutive cohort of patients under a blood saving protocol using tranexamic acid.

MATERIALS & METHODS: A prospective study of 148 patients with unilateral TKA studied. These patients received 3 doses of tranexamic acid. A first dose of 10mg/kg weight in 100cc saline was slowly infused in 15-20 minutes, before tourniquet release. A second identical dose was administered after 3 hours and third identical dose was administered after 6 hours. Surgical technique, pre- and postoperative management criteria were the same between both groups. Variables under comparison included hematocrit and hemoglobin determinations, visible blood loss, transfusion requirements, and additional costs generated by transfusion.

Study Design: Hospital based prospective study

Study area: People residing in and around Prakasam district, Andhra Pradesh.

Study Population: Old age people between 50 to 80 years of age.

Study Period: August 2012 and July 2014, and the control series was included in the prior 6 months.

Inclusion criteria:

1. Unilateral primary osteoarthritis.
2. Unilateral arthritis due to rheumatoid.

Exclusion criteria:

1. Bil. TKR.
2. Severe renal insufficiency.
3. History of coagulopathy or thrombosis, embolism, or both.
4. Previous myocardial infarct.
5. Hematologic disease.
6. Retinopathy.

SURGICAL TECHNIQUE: Limited anterior midline incision followed by parapatelar medial approach with patellar eversion and minimally invasive surgical instrumentation were used in all cases.

One single intraarticular drain was used per surgery, at atmospheric pressure without vacuum, opened one hour after skin closure and systematically retrieved after 48hours. Tourniquet release occurred after wound closure and knee bandage applied in all cases. Antibiotic prophylaxis included cephalosporin 2gr 1 hour before surgery and 1gr/8h during 48 hours. In allergic patients, vancomicin 1gr pre and 1gr/12h postop were used.

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Transfusion was decided in both groups by the Orthopaedic surgeon. The threshold was set at 10.0 gr/dL after 24hours post-operative period. Repeated laboratory tests including both hematocrit and hemoglobin determination were performed preoperatively and postoperatively in the recovery unit, at 12 hours, 24 hours & 48 hours.

OBSERVATIONS & RESULTS: All statistical analysis were performed by using SPSS trail version-16 and in MS-Excel 2007. Qualitative variables were expressed in percentages and quantitative variables were expressed as mean ± Standard deviation. Student- 't' test was applied for comparison between treatment and control groups. All statistical analysis $p<0.05$ was considered as statistically significant.

Variable	Control Group	TXA Group	p-Value
Age	63±5.8	62±6.3	0.432
Sex	30M, 40F	38M, 40F	
Weight	67±4.3	68±6.2	0.342
Tourniquet Time	115±3.2	112±2.3	0.232

Table 1: Comparison of Age, Sex, weight in Control and TXA group

The above table depicts that there was no statistically significance difference in Age, Weight and Tourniquet Time between control and treatment groups.

	Group	N	Mean	Std. Deviation	P value
Preoperative HB	Control	70	13.417	1.6973	0.000
	TXA	78	12.129	1.2977	
Bleeding	Control	70	1506.67	224.982	0.000
	TXA	78	1003.68	217.908	
Transfusion	Control	70	.29	.455	0.019
	TXA	78	.13	.336	

Table 2: Comparison of Preoperative HB, Bleeding, transfusion in Control and TXA group

The above table depicts that there was a statistically significance difference in Pre-operative Hb, amount of Bleeding and Blood transfusion rate between control and treatment groups.

Hb Levels	Group	N	Mean	Std. Deviation	P value
Hb12	Control	70	10.100	1.8834	0.012
	TXA	78	10.803	1.4766	
Hb24	Control	70	9.567	1.8062	0.011
	TXA	78	10.255	1.4461	
Hb48	Control	70	9.093	1.6693	0.011
	TXA	78	9.735	1.3476	

Table 3: Comparison of Hb 12 hours, Hb 24 hours, Hb 48 hours in Control and TXA group

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The above table depicts that there was a statistically significance difference in levels of Haemoglobin at first, second and third post-operative days between control and treatment groups.

Haemtocrit	Group	N	Mean	Std. Deviation	P value
HTC12	Control	70	38.817	2.2824	0.001
	TXA	78	37.485	2.6326	
HTC24	Control	70	34.851	2.3986	0.001
	TXA	78	33.388	2.6898	
HTC48	Control	70	32.67	2.297	0.001
	TXA	78	31.30	2.684	

Table 4: Comparison of Hematocrit 12 hours, Hematocrit 24 hours, hematocrit 48 hours in Control and TXA group

The above table depicts that there was a statistically significance difference in Haematocrit value at first, second and third post-operative days between control and treatment groups.

One patient in the control group suffered from deep periprosthetic infection by S. aureus 4 months after surgery, and required two-stage revision surgery. Two patients in the study group underwent intense nausea related to tranexamic acid infusion in less than 15 minutes. Slow infusion (more than 15 minutes) of tranexamic acid is required to avoid this complication. No patient presented with pulmonary embolism. Special care was taken in the diagnosis of deep venous thrombosis (DVT). Patients with clinical signs of calf circumference increase underwent venous eco-doppler performed by an experienced vascular radiologist. No case of DVT occurred in our study.

DISCUSSION: Different strategies have been established to decrease the risk of allogenic blood transfusion in the postoperative patient. In our study, we significantly decreased the risk of allogenic blood transfusion through a protocol that included three doses of tranexamic acid. Other techniques include predonation, blood recovery, preoperative treatments, or hemodilution.

The use of pharmacological therapies to reduce blood loss and blood transfusions in surgery has historically been restricted to a few drugs.

Antifibrinolytic agents (aprotinin, tranexamic acid and Epsilon aminocaproic acid) have the best evidence supporting their use, especially in cardiac surgery, liver transplantation and some orthopaedic surgical procedures.

Preoperative autologous blood donation followed by autotransfusion is an expensive procedure with logistic problems in many Hospitals. Furthermore, about 45% predonated units may be discarded due to different reasons.[8] Some authors recommend at least 50% transfusion to support a predonation program.[9] Postoperative blood recovery and reinfusion is an equivalent of autologous donation.[2,10] As the risk of transfusion depends on the preoperative hemoglobin values, preoperative treatments such as erithropoietin and intravenous iron have been proposed to avoid postoperative transfusion.[10,11] Normovolemic hemodilution has been also proposed.[12] consisting on the collection of 1-2 blood units during surgery and reinfusion when hematocrit decreases under 28%. Criticisms include those of reinfusion from blood cell recovery programs, variable patient tolerance, and unnecessary blood collection in those patients not requiring postoperative transfusion, with subsequent discard of these units.

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In the study carried out by Benoni et al, the investigators found 62% risk reduction in patients who required red blood cell transfusion with tranexamic acid[13]

Tourniquet release after wound closure and bandage, proved blood loss decrease in many studies Plugging the intramedullary canal of the femur after introduction of the intramedullary instrumentation guide significantly reduced blood loss in TKR up to 17%. Using drains did not raise the infection rate or local wound complications] In our study we have used Romovac suction drain 16 size and that was removed on second postoperative day.

Although tourniquet decreases TKR intraoperative bleeding, postoperative blood loss occurs due to an increased fibrinolysis in response to exanguination.[5,13] Tranexamic acid inhibits fibrinolysis through a reversible molecular block of lysine union sites in the plasmin, plasminogen, and tissue activator of plasminogen. This antifibrinolytic molecule is 10 times more effective than aminocaproic acid. Effective plasmatic levels are reached 10-15 minutes after infusion, and therapeutic level must be maintained at tourniquet release, being the initial dose administration crucial to efficacy.[3-5,13] A meta-analysis of 8 randomized studies comparing with placebo concluded that TXA use is effective in decreasing allogenic blood transfusion requirements without increasing the thrombosis rate in TKR.[3] In a recent systematic review of randomized trials, the use of antifibrynolytic agents to reduce bleeding and transfusion risk to a 50%, without increasing thromboembolic risk, is well proven.

Previous study carried out by Lemay et al showed significant reduction in number of patients transfused with allogenic red blood cells when TXA was given.

Ekback G found no difference in number of patients who were transfused blood and also in number of units of blood transfused in control and test group.

In our study there was a significant difference noted, In the amount of blood loss, number of patients transfused and the number of transfusions between the two groups.

In our experience, protocol with tranexamic acid administration in three doses of 10mg/kg, the first dose infused 15-20 minutes before tourniquet release, and repeated after 3 hours & 6 hours. Virtually revoked the need of transfusion in our series, from a rate of 29% in the control group to 13% in the treatment group, while the visible bleeding in the 24 hours drainage also decreases from 1506 cc in the control group to 1003cc in the treatment group. Our conjoined strategy shows notable results in restricting transfusion requirements, and its use is simple and safe, not increasing thromboembolic complications in our hands.

Based on this study we can conclude that three doses of IV tranexamic acid of 10mg/kg, can be used in TKR procedures with proven effectiveness and efficiency to decrease postoperative blood loss in patients undergoing TKR.

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