EFFECT OF INTRA ARTICULAR TRANEXAMIC ACID AT DIFFERENT DOSES IN UNILATERAL TOTAL KNEE ARTHROPLASTY

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ABSTRAK

Pengenalan: Asid tranexamic biasanya digunakan untuk mengurangkan pendarahan semasa pembedahan gigi dan jantung. Beberapa kajian menunjukkan kesan yang sama dalam pembedahan penggantian sendi lutut. Tetapi cara administrasi, rejim and dos yang digunakan adalah berbeza; sama ada di dalam sendi lutut atau intravena, daripada dos 1.5gram hingga 3 gram. Kajian ini adalah di reka untuk membuat perbandingan kesan asid tranexamic yang di beri secara terus kedalam sendi lutut untuk mengurangkan pendarahan semasa pembedahan penggantian sendi lutut penuh (sebelah) untuk 3 dos yang berbeza (1, 2 dan 3 gram).

Kaedah kajian: Kajian ini adalah kajian buta tunggal prospektif secara rawak yang melibatkan 57 orang pesakit, yang menjalani pembedahan penggantian sendi lutut penuh (sebelah) di HUSM. Setiap pesakit menerima dos suntikan secara rawak di dalam sendi lutut samada 1, 2 atau 3 gram asid tranexamic sebelum menutup sendi lutut dan melepaskan jerutan 'tourniquet' pada paha. Pemilihan dos secara rawak adalah melalui perisian laman web pada pautan www.randomization.com. Setiap pesakit menerima isipadu asid tranexamic yang sama iaitu 30 mililiter yang di beri terus ke dalam sendi lutut untuk mengelakkan bacaan pada botol 'redivac' dipengaruhi oleh isipadu asid tranexamic yang berbeza. Kumpulan 1 menerima 1 gram asid tranexamic (yang bersamaan dengan 10 mililiter isipadu) dicampur dengan 20 mililiter air garam isotonik untuk menjadikan isipadu sebanyak 30 mililiter. Kumpulan 2 menerima 2 gram asid tranexamic (yang bersamaan dengan 20 mililiter isipadu) dicampur dengan 30 mililiter air garam isotonik untuk menjadikan isipadu sebanyak 30 mililiter Kumpulan 3 menerima 3 gram asid tranexamic (yang bersamaan dengan 30 mililiter isipadu). Satu saluran tiub bersaiz 12 di masukkan ke dalam sendi lutut setiap pesakit dan disambungkan kepada satu botol pengumpul 'redivac'. Data yang dikumpulkan adalah

bacaan haemoglobin dan haematokrit sebelum pembedahan dan 48 jam selepas pembedahan, dan juga jumlah pendarahan di dalam botol pengumpul 'redivac' pada 24 dan 48 jam selepas pembedahan. Bagi ke tiga-tiga kumpulan pesakit, perbezaan purata haemoglobin dan haematocrit sama ada sebelum dan selepas pembedahan, dan juga jumlah purata pendarahan di dalam botol pengumpul pada 24 dan 48 jam selepas pembedahan dikira dan dianalisis melalui SPSS versi 20.0, dan dibandingkan menggunakan analisis ANOVA sehala.

Keputusan: Perbezaan purata bacaan haemoglobin antara sebelum dan selepas pembedahan bagi kumpulan 1, 2 dan 3 gram adalah masing-masing 1.36g/dL,1.40g/dL and 1.23g/dL (nilai p 0.747). Perbezaan purata bacaan haematokrit antara sebelum dan selepas pembedahan bagi kumpulan 1, 2 dan 3 gram adalah masing-masing 4.15%.4.26% and 4.27% (nilai p 0.950) Perbezaan purata bagi jumlah pendarahan di dalam tiub 48 jam selepas pembedahan bagi kumpulan 1,2 dan 3 gram adalah masing-masing 336.84 mL,313.68 mL and 263.68 mL (nilai p 0.195).

Kesimpulan: Tiada perbezaan yang ketara pada jumlah pendarahan di antara ke tiga tiga dos asid tranexamic (1, 2, atau 3 gram) apabila digunakan ke atas pesakit yang menjalani penggantian sendi lutut (sebelah), justeru memberi satu alternative untuk kaedah penjimatan kos.

ABSTRACT

Introduction: Tranexamic acid is routinely used to reduce blood loss in some dental and cardiac surgeries. Several studies have demonstrated similar effect in total knee arthroplasty surgery, but the route of administration, regimen used and dosage have been quite variable, ranging from single intra-articular dose of 1.5 gram to a triple intravenous dose of 3 grams. This study has been designed to compare the effect of intra-articular irrigation of tranexamic acid in reducing blood loss in unilateral total knee arthroplasty surgery at 3 different doses (1, 2 and 3 grams).

Methodology: This was a prospective, randomised, single blinded study involving 57 patients, undergoing unilateral total knee replacement surgery in HUSM. Each patient received a randomised intra-articular dose of either 1 , 2 or 3 grams of tranexamic acid before joint closure and tourniquet release. Randomisation was done by a web-based software. Each patient received the same volume inside their knee joint (tranexamic acid + normal saline made up to 30 mL). Group 1 received 1 gram of tranexamic acid, group 2 received 2 grams of tranexamic acid and group 3 received 3 grams of tranexamic acid. An intra-articular drain size 12 was inserted for each patient and connected to the vacuum drain bottle which was opened 4 hours after surgery for tamponade effect. The pre-operative and 48 hours post-operative haemoglobin and haematocrit level, as well as the volume of drain output at 24 and 48 hours were recorded for each patient. The mean difference between pre-operative and post-operative haemoglobin and haematocrit level and the mean volume of drain output at 24 and 48 hours were calculated and analysed by SPSS version 20.0 and compared using one way ANOVA analysis.

Results: The mean difference between pre-operative and post-operative haemoglobin for group 1, 2 and 3 grams were 1.36g/dL,1.40g/dL and 1.23g/dL respectively (p value 0.747).The mean difference between preoperative and postoperative haematocrit for group 1,2 and 3 grams were 4.15%.4.26% and 4.27% respectively (p value 0.950). The mean volume of drain output at 48 hours for group 1,2 and 3 grams were 336.84 mL,313.68 mL and 263.68 mL respectively(p value 0.195).

Conclusions: There was no significant difference in the amount of blood loss among the 3 doses of tranexamic acid (1, 2 or 3 grams) when it was used as a single intra-articular administration before wound closure in unilateral total knee arthroplasty. This can turn out to be a cost effective finding in the long run for the inpatient management of those undergoing TKR.

Keywords: Intra-articular Tranexamic acid, Unilateral TKR, blood loss

Chapter 1

INTRODUCTION

1.1 INTRODUCTION

The perioperative amount of blood loss among patients who undergo total knee arthroplasty surgery is a major cause of concern. It has been estimated that the blood loss in those patients could vary between 800-1800 ml per patient(1). The process of fibrinolysis has been attributed to the surgical trauma itself(2, 3) Application of a pneumatic tourniquet during the surgery increases it further and contributes to the amount of blood that is lost in the perioperative period(4).By competitively blocking the lysine binding site of plasminogen, tranexamic acid inhibits the process of fibrinolysis(5).

It was first reported that blood transfusion requirement and blood loss were both reduced after total knee arthroplasty when tranexamic acid was used intravenously by Benoni et al(6). Four routes of administration of tranexamic acid have been described to reduce blood loss in total knee arthroplasty surgery(7); intramuscular, oral, intravenous, and intra-articular. Intravenous injection of tranexamic acid significantly decreases the amount of blood loss by 29-45% in patients undergoing cardiac surgery with coronary bypass(8).This has marked the beginning of numerous studies which have been conducted and eventually demonstrated the well-established role played by tranexamic acid in reducing the blood loss in joint replacement surgeries(7, 9) .

However, because of concerns regarding the safety of intravenous administration of tranexamic acid and the risks of venous thromboembolic conditions such as deep vein thrombosis of the lower limbs and pulmonary embolism to develop in patients who are at high risk of developing it, has prevented the global usage of that particular drug in total knee arthroplasty(10). Previous studies on the safety and pharmacology of tranexamic acid have been carried out and tranexamic acid has been found to be a drug of low acute toxicity. Even

in patients who received tranexamic acid while undergoing oral and cardiac surgery, the levels of tranexamic acid have been found to be minimal in the systemic circulation and not associated with clinically important thromboembolic manifestations(11)

Undoubtedly, tranexamic acid has proven its efficacy in reducing blood loss and blood transfusion rate in different fields as mentioned above but the debate is still open regarding its optimal regimen to be used in total knee arthroplasty. Different studies have been carried out by administering tranexamic acid both intravenously and locally(11)but so far different authors have come up with different doses and regimes. One of these studies by Wong et al was done by giving topical tranexamic acid before joint closure in primary TKR at 2 different doses of 1.5 and 3 grams and comparing it with a placebo group(11). He did not find any significant difference in the volume of blood loss in those patients who received 1.5 and 3 grams of tranexamic acid respectively but however his study showed that those patients who received tranexamic acid had significantly less blood loss as compared to the placebo group(11).

Taking the safety issue of tranexamic acid mentioned previously (venous thromboembolism) into consideration, this prospective randomised single blinded study has been designed to compare the effect on the amount of blood loss in those patients undergoing primary unilateral total knee replacement when tranexamic acid is used as a single intraarticular dose before wound closure at 3 different doses of 1, 2 and 3 grams respectively. It will be ideal to be able to reduce the amount of bleeding and rate of blood transfusion by using the most cost effective intra articular dose of tranexamic acid without exposing the patient to the risk associated with intravenous injection. This study did not include a control group because previous comparative studies has already clearly demonstrated the benefit of intra-articular

tranexamic acid in reducing blood loss in TKR surgery when compared to intra-articular administration of placebo(11).

Chapter 2

OBJECTIVES OF THE STUDY

2.1 General Objectives

To compare the difference in blood loss among 3 groups of patients, each receiving 3 different doses of intra-articular tranexamic acid before joint and wound closure during total knee arthroplasty surgery (1 gram, 2 grams and 3 grams of tranexamic acid).

2.2 Specific Objectives

1. To compare the difference in mean haemoglobin level pre and post-operatively among 3 groups of patients receiving 1 gram,2 grams and 3 grams of tranexamic acid respectively.

2. To compare the difference in mean packed cell volume (hematocrit) pre and post-operatively among 3 groups of patients receiving 1 gram, 2 grams and 3 grams of tranexamic acid respectively.

3. To compare the difference in drain output volume post-operatively among 3 groups of patients receiving 1 gram,2 grams and 3 grams of tranexamic acid respectively

Chapter 3

MANUSCRIPT

3.1 TITLE: EFFECT OF INTRA ARTICULAR TRANEXAMIC ACID AT DIFFERENT DOSES IN UNILATERAL TOTAL KNEE ARTHROPLASTY

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3.2 ABSTRACT

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Methodology: This was a prospective, randomised, single blinded study involving 57 patients, undergoing unilateral total knee replacement surgery in HUSM. Each patient received a randomised intra-articular dose of either 1 , 2 or 3 grams of tranexamic acid before joint and wound closure and tourniquet release (Randomisation done by web-based software at www.randomization.com).All patients received the same volume(30 mL) inside their knee joint so that the drain volume reading is not influenced by different volumes injected for each group . Group 1 received 1 gram of tranexamic acid made up to 30 mL with normal saline. Group 2 received 2 grams of tranexamic acid made up to 30 mL with normal saline and group 3 received 3 grams of tranexamic acid which is already of 30 mL volume. An intra-articular drain size 12 was inserted for each patient and connected to the vacuum drain bottle. The pre-operative and 48 hours post-operative haemoglobin and haematocrit level, as well as the volume of drain output at 24 and 48 hours were recorded for each patient. The mean difference between pre-operative and post-operative haemoglobin and hematocrit level and

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Conclusions: There was no significant difference in the amount of blood loss among the 3 doses of tranexamic acid (1, 2 or 3grams) when it was used as a single intra-articular injection before wound closure in unilateral total knee arthroplasty. This can turn out to be a cost effective finding in the long run for the in-patient management of those undergoing TKR.

Keywords: Intra-articular Tranexamic acid, Unilateral TKR, Blood Loss

3.3 INTRODUCTION

The perioperative amount of blood loss among patients who undergo total knee arthroplasty surgery is a major cause of concern. It has been estimated that the blood loss in those patients could vary between 800-1800 ml per patient(1). The process of fibrinolysis has been attributed to the surgical trauma itself(2, 3). The usage of a pneumatic tourniquet during the surgery increases it further and contributes to the amount of blood that is lost in the perioperative period(4).By competitively blocking the lysine binding site of plasminogen, tranexamic acid inhibits the process of fibrinolysis(5).

It was first reported that blood transfusion requirement and blood loss were both reduced after total knee arthroplasty when tranexamic acid was used intravenously by Benoni et al(2). Four routes of administration of tranexamic acid have been described to reduce blood loss in total knee arthroplasty surgery; intramuscular, oral, intravenous, and intra-articular(7). Intravenous injection of tranexamic acid significantly decreases the amount of blood loss by 29-45% in patients undergoing cardiac surgery with coronary bypass(8).This has marked the beginning of numerous studies which have been conducted and eventually demonstrated the well-established role played by tranexamic acid in reducing the blood loss in joint replacement surgeries(7, 9) .

However, because of concerns regarding the safety of intravenous administration of tranexamic acid and the risks of venous thromboembolic conditions such as deep vein thrombosis of the lower limbs and pulmonary embolism to develop in patients who are at high risk of developing it, has prevented the global usage of that particular drug in total knee arthroplasty(10). Previous studies on the safety and pharmacology of tranexamic acid have

been carried out and tranexamic acid has been found to be a drug of low acute toxicity. In patients who received tranexamic acid while undergoing oral and cardiac surgery, the levels of tranexamic acid have been found to be minimal in the systemic circulation and not associated with clinically important thromboembolic manifestations(11)

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Taking the safety issue of tranexamic acid mentioned previously (venous thromboembolism) into consideration, this prospective randomised single blinded study has been designed to compare the effect on the amount of blood loss in those patients undergoing primary unilateral total knee replacement when tranexamic acid is used as a single intraarticular dose before wound closure at 3 different doses of 1, 2 and 3 grams respectively. It will be ideal to be able to reduce the amount of bleeding and rate of blood transfusion by using the most cost effective intra articular dose of tranexamic acid without exposing the patient to the risk associated with intravenous injection. This study did not include a control

group because previous comparative studies has already clearly demonstrated the benefit of intra-articular tranexamic acid in reducing blood loss in TKR surgery when compared to intra-articular administration of placebo(11).

3.4 METHODOLOGY

This was a prospective, single blinded, randomised clinical trial including 57 patients who were scheduled and consented to undergo unilateral total knee replacement surgery in HUSM. Patients aged 40 to 85 years; patients with primary knee osteoarthritis and patients with haemoglobin level ≥10g/dL were included. Patients with pre-operative usage of anticoagulant within 7 days of surgery; history of arterial or venous thromboembolic disease like pulmonary embolism, cerebrovascular accident, deep vein thrombosis; patients with fibrinolytic disorder requiring antifibrinolytic treatment; preoperative hepatic or renal dysfunction; patients with secondary osteoarthritis e.g. gouty and rheumatoid arthritis; patients who are immunocompromised secondary to medical conditions such as uncontrolled diabetes mellitus, chronic infection such as HIV, Tb and viral hepatitis or due to medication such as prolonged use of steroids were excluded from this study.

The 57 patients who were included in this were numbered according to the sample size. A randomised dose of either 1 or 2 or 3 grams of tranexamic acid was allocated to each patient according to a web based sofftware. Blood was collected pre-operatively to check for the haemoglobin and haematocrit levels for each patient. Both values were recorded. All surgeries were performed under spinal/epidural anaesthesia by our 2 arthroplasty surgeons according to their routine standard techniques. After elevation of the limb and exsanguination with an Esmarch bandage, the tourniquet was inflated to 350 mm Hg. A midline skin incision followed by a paramedian arthrotomy approach was used for all patients. Cement was used for fixation of the prosthesis. After cementing the implant, haemostasis was secured followed by thorough joint washout. The polyethylene liner was then inserted along with an intra-articular drain size 12. The tranexamic acid was then irrigated directly inside the knee joint before joint and wound closure. For group 1, the patients received 1 gram of tranexamic acid

made up to 30 ml with normal saline. Group 2 received 2 grams of tranexamic acid made up to 30 ml with normal saline and group 3 received 3 grams of tranexamic acid, which is already 30 mL in volume. The drain tube was then connected to vacuum bottle and all drains were opened 4 hours post-operatively for tamponade effect as per the routine practice in HUSM. The volume which each patient received inside was purposely made same for all the patients so that the drain output volume would not be affected by different volumes of different doses. Tourniquet was released after application of dressing at the end of the surgery. The drain output volumes were recorded at 24 and 48 post-operatively and blood was collected after 48 hours of operation for post-operative haemoglobin and haematocrit levels. Data collection was completed by 48 hours post-operatively in every case.

Our post-operative protocol was same for all patients. Continuous passive motion was started on day 3 after surgery. Patients were made to stand on day 3 and discharged on day 5 after surgery. Post-operatively all patients were started on mechanical prophylaxis immediately for DVT prophylaxis (calf pump) and pharmacological prophylaxis was started after 48 hours, once epidural catheter was removed. All patients were monitored for DVT and thromboembolic complications during their hospital.

Randomisation

Each patient was numbered according to the sample size and each one received a randomised dose of either 1 or 2 or 3 grams of tranexamic acid. Randomisation was done using a web based software at www.randomization.com where patients were given numbers from 1 to 57 and each number was allocated the dose of tranexamic acid that was administered inside their knee joint. Seed number: 25041.

Statistical analysis

For data entry and analysis, SPSS version 20.0 was used. One way ANOVA analysis was used to compare the difference in the mean drop in haemoglobin, mean drop in haematocrit, mean drain output volume at 24 and 48 hours after surgery among the 3 different groups. For correlation between drop in haemoglobin level and amount of drain output for each group, Pearson's correlation analysis was used. P value of less than 0.05 was considered significant.

3.5 RESULTS

Table i: Mean drop in haemoglobin, mean drop in hematocrit and the mean drain volumes at 24 and 48 hours for group of 1 gram, 2 grams and 3 grams tranexamic acid.

Group	Mean drop in Hb (g/dL)	Mean drop in hematocrit (%)	Mean drain volume at 24 hours(mL)	Mean drain volume at 48 hours(mL)
1 gram	1.36	4.15	232.11	336.84
2 grams	1.40	4.26	207.89	313.68
3 grams	1.23	4.27	169.67	263.68
p value	0.747	0.095	0.190	0.194

57 patients were included in this study, 41 females and 16 males. All 57 patients were randomized into 3 groups of 1, 2 and 3 grams with 19 patients in each group.

The mean drop in haemoglobin for group 1, 2 ad 3 grams were 1.36g/dL, 1.40 g/dL and 1.23g/dL respectively (p value 0.747). The mean drop in hematocrit for group 1, 2 and 3 grams were 4.15%, 4.26% and 4.27% respectively (p value 0.095). The mean drain volume for group 1, 2 and 3 grams at 24 hours were 232.11 mL, 207.89 mL and 169.67 mL respectively (p value 0.190). The mean drain volume at 48 hours for group 1, 2 and 3 were 336.84 mL, 313.68 mL and 263.68 mL respectively (p value 0.194).

1 patient from group of 1 gram sustained intra-operative fracture of her tibial condyle and was augmented with metal block. Weight bearing was delayed in her case. She was still included in this study and her drop in haemoglobin was 2.4 g/dL, drop in hematocrit of 1.9% and had a drain volume of 220 mL and 490 mL at 24 and 48 hours.

Table ii: Comparison of the groups by pairs; 1gram vs 2 grams, 2grams vs 3 grams and 3 grams vs 1 gram

Group	Mean drop in Hb (g/dL)	Mean drop in hematocrit (%)	Mean drain volume at 24 hours (mL)	Mean drain volume at 48 hours (mL)
1 g vs 2 g	-0.04	-0.11	24.21	23.16
(p value)	(0.950)	(0.950)	(0.759)	(0.838)
2 g vs 3 g	0.17	-0.01	38.42	50.00
(p value)	(0.748)	(0.950)	(0.503)	(0.443)
3 g vs 1 g	-0.13	0.12	-62.63	-73.16
(p value)	(0.837)	(0.950)	(0.168)	(0.181)

Comparison of the 3 groups by pairs, showed no significant difference in blood loss among the 3 different doses of tranexamic acid. (p values > 0.05)

3.6 DISCUSSION

In this particular study, tranexamic acid has been administered to each patient at a randomised dosage of either 1, 2 or 3 grams directly inside their knee joint, before joint and wound closure during their total knee arthroplasty surgery with the aim to evaluate and compare the amount of blood that is lost based on the mean drop in haemoglobin and haematocrit level, as well as the mean drain output volume for each group. This study did not include any control group as numerous previous studies have already clearly demonstrated the superiority of intra-articular tranexamic acid over placebo in reducing blood loss in total knee replacement. Another study even concluded that a single intra-articular injection of 3 grams of tranexamic acid was comparable to three intravenous injection of 1 gram each in total knee replacement surgery(4). Both the studies mentioned support the timing of injection intra-operatively and the method by which the tranexamic acid was made up with normal saline before being injected inside the joint(4, 11).All the patients were started on pharmacological prophylaxis of venous thromboembolism after 48 hours of surgery, once epidural catheter were removed. Since all the data collections were completed by 48 hours post-operatively, there was no issue of the data being influenced by the use of prophylactic anticoagulants.

Among the 57 patients, 1 patient from group 1 gram sustained intra-operative tibial condyle fracture and was augmented with metal block. That patient was still included in the study. She had a haemoglobin drop of 2.4g/dL while the mean haemoglobin drop for her group was 1.36g/dL. Her drain output volume at 48 hours (490 mL) was higher than the mean (336.84 mL) for her group. However, this intra-operative complication was less likely to have any significant influence on the results of this study as it was the only case with intra-operative