Clinical Research

Optimal dose of tranexamic acid to prevent bleeding and to decrease transfusion demand in adolescent idiopathic scoliosis patients undergoing operative treatment

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ABSTRACT

Introduction: Tranexamic Acid is an anti-fibrinolytic agent that has been studied previously to show the effect inreducing blood loss in major surgery. However, the dosage of the tranexamic acid has not been established.

Methods: This is a prospective single-center double blind randomized study and was performed in the UKM Medical Centre. Total of thirty-six patients with Adolescence Idiopathic Scoliosis was consented and eligible to join the study. The patients were divided into two groups of eighteen patients and each group was given different doses of tranexamic acid. Blood investigation of hemoglobin, hematocrit, platelets, fibrinogen and D-dimer was conductedfor analysis, and blood loss perioperatively and blood transfusion provided were recorded and compared.

Results: There was significant difference in blood loss and blood transfusion between the two groups. The group with high dose of tranexamic acid (50mg/kg) has less blood loss (20%) compared to the group with low dose (25mg/kg). The high dose group also showed reduced risk of blood transfusion (66%) compared to the low dose group. There was no significant difference between the two groups on the level of hemoglobin, hematocrit and platelets post-operatively. There was also no significant effect of tranexamic acid on fibrinogen and D-dimer that were assessedpre-operatively and post-operatively. No signs of reducing level of fibrin degradation products after bolus administration of tranexamic acid.

Conclusion: High dose administration of tranexamic acid showed lower blood loss, hence lowering the demand of blood transfusion compared to the low dose.

ABSTRAK

Pendahuluan: *Asam traneksamat merupakan agen anti-fibrinolitik yang telah dikaji sebelumnya untuk mengetahui efek obat terhadap kehilangan darah pada suatu operasi besar. Akan tetapi, dosis penggunaan asam traneksamat belum diketahui secara pasti*

Metode: *Rancangan penelitian ini menggunakan desain* prospective single-center double blind randomized study *dan dilakukan di* UKM Medical Center. *Total 36 pasien penyandang* Adolescent Idiopathic Scoliosis *(AIS) telah dinyatakan layak untuk menjadi subjek penelitian. Pasien dibagi menjadi dua kelompok dan delapan belas pasien pada setiap kelompok diberikan dosis asam traneksamat berbeda. Pengukuran komponen hemoglobin, hematokrit, platelet, fibrinogen dan D-dimer dilakukan untuk melakukan analisis kehilangan darah pada periode peri-operatif, dan transfuse darah dilakukan setelah pengambilan sampel darah yang kemudian dilakukan pembandingan.*

Hasil: *Terdapat perbedaan yang bermakna terhadap kehilangan darah dan keperluan transfuse darah pada kedua kelompok. Kelompok yang mendapat asam traneksamat dosistinggi (50mg/kg) mengalami kehilangan darah lebih sedikit (20%) dibandingkan dengan kelompok yang mendapat asam traneksamat dosis rendah (25mg/kg). Kelompok dosis tinggi juga menunjukkan risiko kebutuhan transfusi yang lebih kecil (66%) dibandingkan dengan kelompok dosis rendah. Tidak terdapat perbedaan yang bermakna pada kedua kelompok dari nilai hemoglobin, hematokrit, dan platelet pada kondisi pasca-operasi dan juga tidak terdapat efek bermakna asam traneksamat terhadap fibrinogen dan D-dimer yang diperiksakan pada kondisi pra-operasi dan pasca-operasi. Tidak ditemukan adanya penurunan produk degenerasi fibrin setelah pemberian asam traneksamat secara bolus.*

Kesimpulan: *Pemberian dosis tinggi asam traneksamat menunjukkan kehilangan darah yang lebih sedikit serta kebutuhan transfusi yang lebih kecil dibandingkan dengan pemberian asam traneksamat dosis rendah.*

Keywords: High dose, low dose, tranexamic acid, blood loss, blood transfusion

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INTRODUCTION

Adolescent Idiopathic Scoliosis (AIS) is a spine deformity commonly found in teenagers with the incidenceof 0.45%-5.2%.[1] Operative procedure for AIS is considered to be a major one, which is closely relatedtoa number of complications, such as blood loss.Tranexamic acid is an anti-fibrinolytic agent that has been studied to show the effect to reduce blood loss in major surgery.[1-5] However, the most effective dosage of tranexamic acid has not been established.

Extensive tissue trauma may lead to excessive fibrinolysis, contributing to coagulopathy of severely injured patients. An adolescent Idiopathic Scoliosis patient undergoing posterior instrumentation surgery creates extended wound that may mimic trauma condition. As one form of management, lysine analogues have been available for decades. They have been used as an adjunct therapy/ prophylaxis in bleeding for various indications.[6]

Tranexamic acid is the analog of lysine, a synthetic antifibrinolytic agent, which competitively inhibits activation of plasminogen by blocking its lysine-binding sites. Previous studies found that intraoperative administratonof tranexamic acid is effective in spine surgeries to reduce blood loss and the need for transfusion.[1-5]However, to the best of our knowledge, no previous studies addressed the effective dosage of tranexamic acid. The specific objective of this study is to determine whether administration of single dose of Tranexamic Acid of 50mg/kg before surgery gives significant reduction in blood loss and reduction in the requirement for blood transfusion compared to single dose of Tranexamic Acid of 25mg/kg in Female Adolescent Idiopathic Scoliosis patients undergoing corrective surgery.

METHODS

This is a prospective single-centered, double blind, randomized study conducted in UniversitasKebangsaan Malaysia (UKM) Medical Centre. Total of thirty-six patients with Adolescence Idiopathic Scoliosis were eligible to join the study. All patients and or their families gave their informed consents. The patients were divided into two groups consisting of eighteen patients each.

The inclusion criteria in patient selection in this study were female adolescent (age 12-18) with idiopathic scoliosis and Cobbs angle of 40^{o}-70^{o}, who were going to havecorrective scoliosis surgery. The exclusion criteria were Patients with a history of allergy to Tranexamic Acid, patient age <12 years old or >18 years old, bleeding diathesis and/or pre-operative platelet counts of<150,000/mm^3,pre-operative anemia, i.e., hemoglobin <11 g/dl, rejectionof blood products i.e., Jehovah's witnesses, fibrinolytic disorders requiring intraoperative antifibrinolytic treatment, severe pulmonary disease, i.e., forced expiratory volume in1min <50% normal, and the patient and/or the family refuse to join the study. If intraoperative surgical complications, such as uncontrollable surgical bleeding from broken vertebral laminae, or dural tears, etc., occurred, the patients were excluded from the study.

On admission, patients were prepared as usual for preoperative assessment, pre-operative FBC, and Fibrinogen and D-dimer sampleswere taken. Patients who agreed to join the study were listed. Twenty patientswere randomly assigned to receive 25mg/ kg BW of tranexamic acid injection after anesthetic induction before the surgical incision was made. The other 20 received 50mg/kg BW of tranexamic acid. All solutions were put in identical 30 ml syringes and labeled, and the patients were given bolus.Both surgeon and anesthesiologist were blindedtothe syringe samples. All patients were administered general anaesthesia with controlled MAP 60-70 mmHg until the end of the spinal instrumentation. All patients were positioned prone on a Jackson table or Hall-Relton frame with the abdomen free. Radivac suction drain (10G) was applied at end of the surgery.Surgery time was not limited since it would be depended on the type of scoliosis and level of fusion.Neuromonitoring was used to monitor the peripheral nerve function.Drain removal was conducted 48 hours post-surgery or if < 20 ml. The trigger point for blood transfusion was Hb<8g/dL and HCT<25% post-operatively or according to the surgeon decision.Post-operative FBC, Fibrinogen, and D-dimer were taken for data collection.

All blood investigation parameterswere collected, the total blood loss was recorded from the amount of blood loss intraoperatively, which was taken by averaging the data from the suction pool and the blood-soaked gauze weighed with the weighing scale available in the operation theatre. The total blood loss was also estimated by the anaesthetist from the suction pool, the blood-soaked gauze and the drape linen that being used during

operation. After operation, the amount of blood collected from the drain, which was only fresh blood,was recorded. The blood transfusion was recorded and counted by the pint of blood bag. The average of 1 pint of blood bag is 300-350 ml of blood. All data findings wereinput into IBM SSPS Statistics 20. The statistical analysis including t-test, paired t-test and Correlation Pearson, and the probability (P) values less than 0.05 will be considered as statistically significant.

RESULTS

From 36 eligible patients, the mean and standard deviation of age for the group receiving 25 mg/kg BW of tranexamic acid and 50 mg/kg BW were14 ± 1.49 and 13.41 ± 1.04 ($p > 0.05$), respectively. The preoperative hemoglobin level (g/dL) for the group of 25 mg/kg and 50 mg/kg were13.02 ± 0.85 and 13.41 ± 1.04, respectively. After 6 hours, the haemoglobin level (g/dL) decreased in both groups: 9.65 ± 1.11 and 9.76 ± 1.23 ($p > 0.05$), respectively. In 24 hours the hemoglobin level increased again to the levelof 10.20 ± 0.97 and 10.07 ± 0.97 ($p > 0.05$), respectively. Meanwhile, the amount of bleeding (mL) for the group of 25 mg/kg BW and 50 mg/kg BW were1179. 06 ± 208.50 and 996.06 ± 183.58 ($p < 0.05$), respectively. The amount of blood transfusion needed in Flacon for the group of 25 mg/kg BW and 50 mg/kg BW were1.50 ± 0.78 and 0.56 ± 0.61 ($p < 0.05$),

Table 1. The description of all variables measured in both groups.

Variabel	Group: Tranexamic acid 25 mg/kg BW (n=18) (Mean ± SD)	Group: Tranexamic acid 50 mg/kg BW (n=18) (Mean ± SD)	p value
Age (Year)	14 ± 1.49	15.22 ± 1.98	
HemoglobinLevel (g/dL)			
Pre-op	13.02 ± 0.85	13.41 ± 1.04	
6 hr	9.65 ± 1.11	9.76 ± 1.23	
24 hr	10.20 ± 0.97	10.07 ± 0.97	
Hematocrit Level (g/dL)			
Pre-op	8.94 ± 2.83	39.18 ± 2.93	
6 hr	28.48 ± 3.19	28.94 ± 3.59	
24 hr	29.82 ± 3.10	29.27 ± 2.54	
Thrombocyte Level (uL)			
Pre-op	257.89 ± 49.05	271.06 ± 47.08	
6 hr	189.89 ± 65.60	224.83 ± 48.24	0.22
24 hr	157.44 ± 51.04	197.61 ± 38.31	0.68
Fibrinogen Level (mg/dL)			
Pre-op	2.51 ± 0.57	2.36 ± 0.45	0.30
24 hr	2.97 ± 0.59	3.06 ± 0.67	
D-Dimer Level (ug/mL)			
Pre-op	0.24 ± 0.09		0.14
24 hr	0.43 ± 0.22		
Post-operative blood loss (mL)	1179. 06 ± 208.50	996.06 ± 183.58	0.009
Blood transfusion needed (Fls)	1.50 ± 0.78	0.56 ± 0.61	0.001

respectively. The description of basic demography and all measurements conducted in this study are shown in Table 1. Graphs depicting comparison of both groups are presentedin Figure 1, 2, 3, 4.

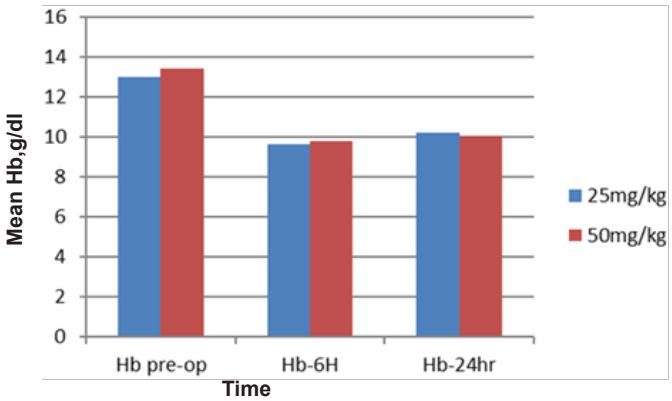

Figure 1. Result of haemoglobin analysis as measured in different times

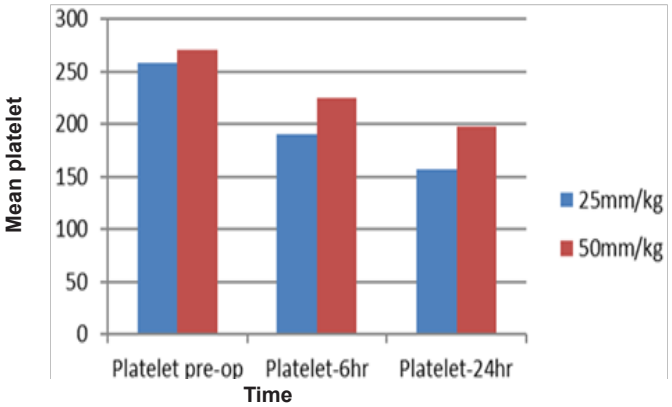

Figure 2. Result of platelet analysis as measured in different times

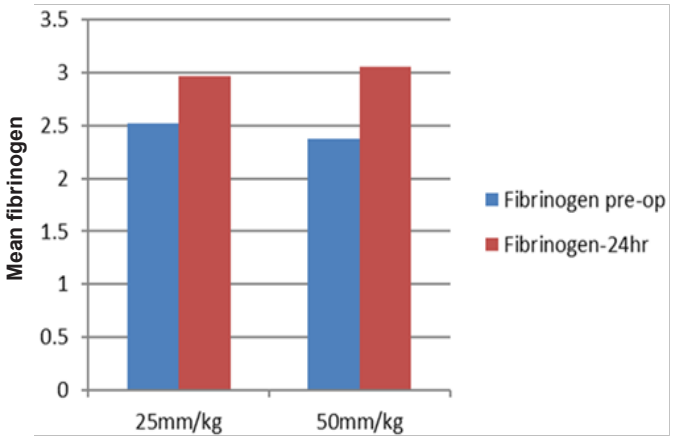

Figure 3. Comparison of fibrinogen level in both groups, before surgery and after 24 hours

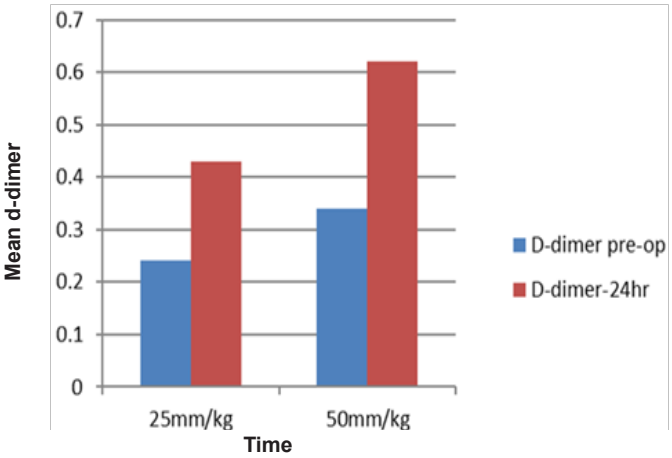

Figure 4. Comparison of d-dimer level in both groups, before surgery and after 24 hours

DISCUSSION

The use of tranexamic acid in major surgeries like AIS has been widely accepted in the practice of spine surgeries. However, the correct dosage, especially for pediatric population, has not been established yet. In our center, tranexamic acid is not included in the basic medication package administered to the patients. Its use is still limited to surgeon or anesthesiologist's decision before performing any induction.

There were three previous studies evaluating the role of tranexamic acid in scoliosis surgeries.[2-4] Grant,*et al*., compared the use of tranexamic acid in low dose and high dose in pediatric scoliosis surgery, with the infusion of low dose tranexamic acid of 10 mg/kg BW as the loading dose, continued with 1 mg/kg BW and the infusion of high dose of tranexamic acid of 20 mg/kg BW as the loading dose, continued with 10 mg/kg BW dose.[3] This study did not elaborate the basis of reasoning for the chosen regimen and the method of administration. Moreover, there were no significant side effects for the tranexamic acid administration.

This study was performed to evaluate the performance of two dosages of tranexamic acid. Tranexamic acid has a role in overcoming blood loss due to its antifibrinolytic activity. The two dosages evaluated were 25 mg/kg BW and 50 mg/kg BW given bolus (loading dose) after induction. The half life of tranexamic acid after intravenous administration of 1 g dosage is two hours for terminal elimination in normal kidney function. The surgical duration of scoliosis performed in this hospital is typically around150 minutes, thus we concluded that one

loading dose should be enough to produce the positive effect of decreasing blood loss and the need of blood transfusion.

We found that the reduction inhemoglobin, hematocrit, and platelet levels in all groups werenot statistically significant. This is in accordance with the study by Neilipovits, *et al*.[4] However, there was significant difference in terms of the need of blood transfusion. Tranexamic acid dose of 50 mg/kg BW, only needed an average of 0.56 flacon of blood transfusion, and 1.5 flacon was needed for the group using the dose of 25 mg/kg BW. On the contrary, Grant,*et al*.,reportedthat the peri-operative need for blood transfusion were687,9 ± 778.1 ml (approximately 2 blood flacons) for the high dose and 1372.6 ± 1077.3 mL (approximately 3-4 blood flacons) for the low dose.[3] Only 1 patient from the group of 25 mg/kg BW dose needed intraoperative blood transfusion, and another patient from the same group received 2 Flacons of blood transfusion after 36 hours. All other patients received blood transfusion 24 hours after surgery in the ward.

The group with high dose had 20% more bleeding than the one with low dose. Previous study reported that higher blood loss of 41% in the group receiving placebo compared to the group receiving tranexamic acid.[1]To the best of our knowledge, no previous studies ever investigated the blood loss in major surgeries.

The preoperative and postoperative level of fibrinogen and D-dimer showed no significant difference between the two groups. This is in accordance with the study of Sethna, et al.[5]During the period of this study, all patients hadsimilar period of hospital stay. No complications such as allergy of tranexamic acid, wound dehiscence or signs of infection were reported. The patients managed to ambulate independently.

CONCLUSION

Based on the results of this study, when given in a higher dose (50mg/kg BW) tranexamic acid has shown to have significant effect in reducing the blood loss and the need for blood transfusion compared to the lower dose (25mg/kg BW). There is no significant difference in tranexamic acid administration for both groups in terms of hemoglobin, hematocrit, and platelet levels at all time of blood assay. The limitation of this study was that the main indicators for blood transfusion wereonly limited to the level of hemoglobin, hematocrit or platelets or according to the surgeon's decision. The decision was usually based on the patient's clinical condition (e.g. the patient appeared anemic on the physical examination of conjunctiva or palm of the hand) and the vital signs reading. If the patient has tachycardia without any complains regardingthe obvious pain over the operation site, the patient will usually be given transfusion of 1-pint pack cell.

It may be concluded from the reduction of blood loss and the need for blood transfusion after the administration of higher dose of tranexamic acid,along with the absence of major side effects noted during the study period, that tranexamic acid of 50mg/kg BW could be administered to the patients with AIS undergoing surgical correction of deformity.

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