Comparison of Efficacy of High versus Low Dose Tranexamic Acid in Reducing, Perioperative Blood Loss and Transfusion Requirements, in Adolescent Idiopathic Scoliosis - An Analytical Study from Retrospective Data Evaluation

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ABSTRACT

BACKGROUND

Adolescent idiopathic scoliosis (AIS) is defined as a lateral deviation of the spine associated with vertebral rotation in an otherwise healthy person. We wanted to determine if a high dose of tranexamic acid was more efficacious than a low dose in reducing blood loss in adolescent patients undergoing corrective surgery for idiopathic scoliosis, determine the difference in transfusion requirements between the two groups and elucidate the safety profile of high dose tranexamic acid in paediatric patients.

METHODS

This was an analytical study from retrospective data analysis of 60 adolescent patients who underwent scoliosis correction by posterior spinal fusion by a single team of two surgeons in our institution. Group 1 received injection tranexamic acid 10 mg/Kg bolus dose completed 15 minutes before incision followed by infusion at the rate of 1 mg/Kg/hr continued till the end of surgery. Group 2 received tranexamic acid bolus dose of 50 mg/Kg followed by infusion at the rate of 15 mg/Kg/hr. Estimated blood loss and transfusion requirements were compared between the two groups. Data on patient demographics such as age, weight, gender and ASA status were collected. Duration of surgery (skin incision to completion of skin closure) was also noted. Outcome parameters included intraoperative blood loss and the volume of transfused blood.

RESULTS

All 60 patients had similar baseline characteristics and a common clinical diagnosis of adolescent idiopathic scoliosis. Compared to group 1, blood loss was significantly reduced in group 2. (1018.33 mL v/s 491.67 ml, p-value = 0.0001). Also, there was a statistically significant reduction in intraoperative and postoperative transfusion requirements in the high dose group (337.5 mL v/s 597.5 ml, p-value=0.0001). No adverse effects attributable to tranexamic acid, including thromboembolic events, were observed in either group of patients.

CONCLUSIONS

High dose tranexamic acid was found to be a safe, economical and effective intervention to reduce blood loss in idiopathic scoliosis corrective surgery.

KEYWORDS

Adolescent Idiopathic Scoliosis, Tranexamic Acid, Blood Loss, Transfusion, Posterior Spinal Fusion, Scoliosis

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BACKGROUND

Adolescent idiopathic scoliosis (AIS) is defined as a lateral deviation of the spine associated with vertebral rotation in an otherwise healthy person.[1] The treatment options for AIS are observation, bracing, and operation.[2] Surgical correction for adolescent idiopathic scoliosis by posterior approach is often accompanied by significant bleeding. Massive transfusion after excessive haemorrhage is associated with complications such as hypothermia, coagulopathy, and acid-base imbalance. Therefore, prediction and prevention of massive transfusion are necessary to improve the clinical outcome of these patients.[3] Several anaesthetic and surgical techniques have been postulated to influence intra-operative blood loss during surgery namely, the extent of dissection, number of fused vertebrae, duration of surgery, surgical technique, method of instrumentation, site and size of bone graft and phase of operation in which it is obtained, use of epinephrine, degree of muscle relaxation, mean arterial blood pressure and pressure in the inferior vena cava.[4,5,6] Allogeneic blood transfusion carries the risk of transmitting infections (viral and bacterial), haemolytic transfusion reactions, transfusion-related lung injury,[7] and increased hospital costs.[8] Quite a few approaches have been tried, with varying degrees of success, to reduce allogeneic blood transfusion in major surgery. These include storage of autologous blood before the operation, normovolaemic hemodilution, and hypotensive anaesthesia, use of a cell recovery machine and the use of drugs with antifibrinolytic properties, such as aprotinin, epsilon-aminocaproic acid and tranexamic acid.[9,10]

Tranexamic acid is a synthetic lysine-analogue antifibrinolytic that competitively inhibits the activation of plasminogen to plasmin; at high concentrations it non-competitively blocks plasmin, thus, tranexamic acid inhibits the dissolution and degradation of fibrin clots by plasmin.[11] It has been implicated in major surgical specialities including cardiac surgery,[12] trauma[13] and total knee arthroplasty.[14]

Side-Effects / Toxicity

Tranexamic acid is generally well tolerated. The risk of thromboembolic phenomena associated with the use of tranexamic acid has led to caution in its use, particularly in those with other risk factors (e.g. previous thrombotic events, hormonal contraceptive use) but recent studies have failed to prove the role of tranexamic acid in causing venous thrombosis. Seizure activity after tranexamic acid use has also been described, especially in high doses around 100 mg/Kg/hour used in cardiac valve replacement surgeries, although the mechanism for this is yet to be confirmed.[15]

METHODS

The study retrospectively analysed the data of 60 adolescent patients with idiopathic scoliosis who underwent posterior fixation at our hospital, between June 2016 and June 2019. All the surgeries were performed by the same team of two orthopaedic surgeons specialized in spine surgery.

Sample Size Calculation (Mosaad et al)[23]

$$n = \frac{2Sp^2\left(Z_{1-\frac{\alpha}{2}} + Z_{1-\beta}\right)}{Md^2}$$

$$Sp^2 = \frac{S1^2 + S2^2)}{2}$$

Md^2 = mean difference between samples
α = 5%
Power = 80 -1
n_1= 30
n_2= 30

The sample size required for the study, n_1+ n_2= 60.

Ethical committee approval was obtained, and data collected and divided into two groups. Group 1 consisted of 30 patients who received injection tranexamic acid I.V. in a bolus dose of 10 mg/Kg over 30-min, completed 15 minutes before skin incision followed by infusion 1 mg/Kg/hour till the end of surgery. Group 2 received tranexamic acid bolus dose 50 mg/Kg over 30 Min, completed 15 Min before skin incision followed by infusion 15 mg/Kg/hour till the end of surgery.

Inclusion Criteria

1. Patients scheduled for scoliosis correction by posterior approach surgery.
2. Age between 10-19 years.
3. Adolescent onset of disease.
4. ASA status 1 & 2.

Patients with congenital or syndromic scoliosis, previous spine surgery, liver or renal impairment, coagulopathies or patients who received anticoagulant or any drug that may interfere with the study drug were excluded from the study.

Anaesthetic Methods

All patients were evaluated in the pre-anaesthetic clinic before the surgery. Detailed history was taken, and clinical examination conducted. Investigations done were blood routine, platelet count, bleeding time, clotting time, activated partial thromboplastin time (APTT), prothrombin time (PT), liver function test (LFT) and renal function test (RFT). A 12-lead ECG and chest X-ray were taken. 2D echo (M mode) with colour Doppler was performed using Philips EPIQ 7c cardiac ultrasound machine to assess cardiac function. Pulmonary function test to assess respiratory status of each patient was done using Vitalograph Pneumotrac 6800.

All patients were fasted overnight. They were pre medicated with tab Alprazolam 0.25 mg and tab Metoclopramide 10 mg on the night before and the morning of surgery. In the operating room, venous access was secured. Inj. midazolam 0.01-0.2 mg/Kg followed by Inj. fentanyl 2 mcg/Kg given to all patients. Loading dose of dexmedetomidine 1 mcg/Kg was given over 10 minutes. General anaesthesia was induced by propofol 2 mg/Kg, and tracheal intubation was facilitated by atracurium 0.5 mg/Kg. No further dose of atracurium was given. Anesthesia was maintained by the following infusions: Dexmedetomidine 0.2-0.7 mcg/Kg/min, Propofol 50-150 mcg/Kg/min and Fentanyl 0.5-2 mg/Kg/min. All infusions were titrated to maintain a systolic BP of 90-98 mm Hg and MAP 55-60 mm Hg. After cannulation of the left radial artery for autologous blood collection, a loading dose of tranexamic acid was given. 10 mg/Kg in group 1 and 50 mg/Kg in group 2. This was completed in 15 minutes. Following this, tranexamic acid infusion was started at the rate of 1 mg/Kg/hr in group 1 and 15 mg/Kg/hr in group 2 and continued until the end of surgery. Respiratory parameters were adjusted to keep the end-tidal CO2 between 35-40 mm Hg. Normothermia (36.6℃ -37.5℃) was maintained using warm I .V. fluids and forced-air warming devices. Balanced salt solution was infused according to Holliday Segar formula.

The following parameters were recorded

- Demographic characteristics (age, sex, weight, and ASA physical status)
- Time of surgery (time from skin incision till skin closure).
- The total amount of intra-operative blood loss.
- Volume (ml) of blood transfused.

Intra-operative blood loss was measured by adding the volume of blood in the suction canisters, collected blood on surgical drapes and weight of mops and gauzes (one-gram difference between dry and wet mops equaling one mL blood). All fluids added to the surgical field intra-operatively were quantified and deducted from the measured blood loss. Transfusion trigger was set at 9 gm/dl.

Statistical Analysis

After the completion of data collection, data was appropriately coded and entered in Microsoft excel. Analysis of the data was done using the software, Statistical Package for Social Studies (SPSS) version 16.0. Patient baseline characteristics were compared using Student t-test, Wilcoxon test, and Pearson χ 2 test where appropriate. Estimated blood loss and transfusion requirements between groups were compared with Student's t-test. P-value less than 0.05 were considered statistically significant and a p-value of less than 0.01 was considered statistically highly significant.

RESULTS

The patient characteristics are shown in Table 1. There were no statistical differences in preoperative parameters of age, sex, body weight, or diagnosis. Significant differences were not noted in the operation time between the groups. Group 2 (mean 491.67 ml) had significantly less intra-operative blood loss compared with group 1 (mean 1018.33 ml, p-value 0.0001, Table 2). Intra-operative blood loss in the TXA group was reduced by 48% compared with the control group. There was a significant difference in blood transfusion requirement between patients given with low dose and high dose tranexamic acid. In group 1, the mean volume of transfused blood was 597.5 mL whereas, in group 2, the mean volume of transfused blood was 337.5 mL (P-value 0.0001).

From these results, it can be concluded that Group 2 had a significant reduction in intra-operative bleeding and transfusion requirements compared to group 1. None of the patients in both groups exhibited any adverse effect that can be attributed to tranexamic acid.

		Group HD	Group LD	P Value
Age (Years)		13.93 ±1.57	15 ± 1.87	0.264
Sex	Male	5	6	1
	Female	25	24	
ASA	I	23	22	1
	II	7	8	
Weight (Kg)		42.27 ±9.6	42.73 ±6.88	0.83
Surgical Duration		179 ± 15.61	176 ± 13.28	0.372

Table 1. Comparison of Patient Demographics and Surgical Duration between the Two Groups

Variables	Mean	Standard Deviation	T Value	Df	P Value
Blood loss in high dose tranexamic acid group	491.67	235.56	-4.252	58	0.0001
Blood loss in low dose tranexamic acid group	1018.33	636.16			

Table 2. Comparing Blood Loss in Study Subjects with Dose of Tranexamic Acid Given, Independent Sample t-Test

Variables	Mean	Standard Deviation	T Value	Df	P Value
Blood Transfusion Requirement in High Dose Tranexamic Acid Group	337.5	145.74	-4.555	58	0.0001
Blood Transfusion Requirement in Low Dose Tranexamic Acid Group	597.5	276.63			

Table 3. Blood Transfusion Requirement of Study Subjects with Dose of Tranexamic Acid Given, Independent Sample t-Test

DISCUSSION

This study suggested that high dose tranexamic acid (50 mg/Kg bolus followed by 15 mg/Kg/hour) is more efficacious than low dose tranexamic acid 10 mg/Kg bolus followed by 1 mg/Kg/hour (1018 mL in group 1 versus 492 mL in the latter group) in reducing intraoperative bleeding and transfusion requirements (597.5 mL in group 1 v/s. 337.5 mL in group 2).

TXA is a synthetic lysine analogue and a potent antifibrinolytic agent which inhibits both plasminogen and plasmin. It is widely used as a hemostatic agent in clinical

settings. It is included in the WHO list of essential medicines.[16] Tranexamic acid acts by reversible binding and competitive inhibition of the lysine moieties on plasminogen, plasmin, and tissue plasminogen activator (tPA), thereby inhibiting fibrinolysis.[17] It diminishes the binding ability of plasminogen and tPA to fibrin, which subsequently inhibits the activation of plasminogen to plasmin that would otherwise lead to the breakdown of fibrin clots.[18] Also, release of tissue factor and inflammatory mediators during a major surgery can precipitate hyper fibrinolysis, and in turn, increased bleeding. In this context, tranexamic acid may reduce bleeding in a major surgery not only through its antifibrinolytic effect, but also by the inhibition of plasmin formation, which may help prevent inflammation and platelet degradation.[19]

TXA can be administered orally, topically, or intravenously and has a 100% bioavailability. Half-life of 10 mg/Kg I.V. dose is about 80 minutes and peak concentration is attained within 1 hour after administration.[20] TXA is cleared through the renal system, therefore dosage needs to be reduced in patients with kidney disease.

Absolute contraindications for tranexamic acid include pre-existing active thromboembolic disorder, disseminated intravascular coagulation, renal failure, coronary or vascular stent placed within six months to one yr and acute subarachnoid haemorrhage. Relative contraindications include known uncontrolled seizure disorder, renal dysfunction, high risk of venous or arterial thrombosis, or pre-existing coagulopathy or oral anticoagulant treatment.[21]

Various researchers have studied the hemostatic effect of tranexamic acid in major spine surgeries. VM Rocha et al[22] first demonstrated the efficacy of tranexamic acid in reducing perioperative bleeding in thoracolumbar scoliosis correction with posterior instrumentation in pediatric patients. Compared to the control group who received no drug, the test group who received a bolus dose of 100mg/Kg and maintenance dose of 30 mg/Kg/hr with no side effects, reported a significant reduction in bleeding. Mosaad et al[23] compared two different doses of tranexamic acid against the placebo group and suggested that tranexamic acid was beneficial, especially in high dose, in reducing intraoperative bleeding in adult spine surgery. In a larger study group comprising of 116 patients, Johnson DJ et al[19] found that high dose tranexamic acid helped to reduce intraoperative blood loss in pediatric patients undergoing posterior spinal fusion for adolescent-onset scoliosis. Ho Yong Choi et al,[24] in their study on pediatric patients undergoing spine surgeries, concluded that 50 mg/Kg bolus dose significantly reduced bleeding and transfusion requirements in these patients. Sethna NF et al[25] found that high dose tranexamic acid (100 mg/Kg bolus dose) reduced intraoperative bleeding in pediatric spine surgeries compared to placebo, but the transfusion requirements did not vary significantly between the two groups. Adverse effect due to tranexamic acid was not observed in any of these studies.

It must be noted that various researchers had used different doses of tranexamic acid in their respective studies. There are no reliable clinical methods to monitor the effects of tranexamic acid in vivo. Therefore, we have been unable to reach a consensus about the optimum dose of tranexamic acid to reduce intra-operative bleeding and transfusion requirements with minimum side effects. Also, the doses prescribed have not been based on the pharmacological profile of tranexamic acid, but on the institutional protocol of the centre of study. Suboptimal dosing of tranexamic acid with reduced efficacy or inadvertent overdosing and adverse effects could result from this. Clarification is also required about the timing of administration of the drug concerning the surgical duration. Concerns about thromboembolic events with high doses of tranexamic acid remains to be disproved. For want of adequate number of trials on the safety of tranexamic acid in pediatric population, caution must be exercised, especially while administering high doses of this drug to children. Most of the studies have been conducted on small samples, which might have reduced the power of the study. As the studies were conducted over a period of many years, surgical techniques and transfusion protocols might have changed, thus affecting the accuracy of the study results. In a broad category as spine surgery for previous studies on tranexamic acid, the population varied considerably with regards to age, disease process and the type of surgery performed. Even for the same surgical procedure, the number of levels operated, and hence bleeding differed from patient to patient. The surgical skill improves over time, this combined with the fact that higher doses of tranexamic acid were administered for the later cases, would have led to the overestimation of the efficacy of tranexamic acid in controlling intraoperative bleeding in these later cases.

Despite these limitations, however, the hemostatic effect of tranexamic acid in major spine surgeries has been indisputably proven by the studies. Multicentric randomized controlled trials involving a larger number of participants may be utilized in future for a better understanding of the effects of this drug and for determining its optimum dose.Although this was a retrospective analytical study and the possibility of the results being affected by recall bias cannot be ruled out, the study proves that the use of high dose tranexamic acid in surgical correction of adolescent idiopathic scoliosis reduce blood loss. Due to the small sample size, this study may be underpowered to examine the adverse effects of scoliosis. But the strengths of this study are the homogenous patient population, uniform clinical diagnosis and surgical procedure in both groups, and the fact that the surgery was performed by a single team of surgeons.

CONCLUSIONS

Prophylactic use of large dose (50 mg/Kg/hr. bolus followed by 15 mg/Kg/hour maintenance dose) tranexamic acid is a safe, efficacious and cost-effective intervention to reduce bleeding and transfusion requirements in adolescent scoliosis corrective surgery compared to a smaller dose of tranexamic acid (10 mg/Kg bolus followed by 1 mg/Kg/hour

maintenance dose). Thus, to an extent, tranexamic acid helps to prevent the hazards of blood transfusion and operative expenses in these patients. However, we recommend that further research be undertaken in this field to reach a consensus on pharmacokinetic evidence-based dosing rationale for tranexamic acid. Until then, research evidence supports the use of a high dose of tranexamic acid in major spine surgeries such as posterior spine fusion for adolescent idiopathic scoliosis.

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