

**TRANEXAMIC ACID IN PAEDIATRIC SCOLIOSIS SURGERY
(TRIPSS): A PROSPECTIVE RANDOMISED TRIAL
COMPARING HIGH DOSE AND LOW DOSE TRANEXAMIC
ACID IN ADOLESCENT IDIOPATHIC SCOLIOSIS
UNDERGOING POSTERIOR SPINAL FUSION**

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**FACULTY OF MEDICINE
UNIVERSITY OF MALAYA
KUALA LUMPUR**

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FUSION**

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A PROSPECTIVE RANDOMISED TRIAL
COMPARING HIGH DOSE AND LOW DOSE TRANEXAMIC ACID IN
ADOLESCENT IDIOPATHIC SCOLIOSIS UNDERGOING
POSTERIOR SPINAL FUSION**

ABSTRACT

Background: Tranexamic Acid (TXA) is commonly used in scoliosis surgery to reduce the amount surgical blood loss and allogenic blood transfusion requirement. Evidence on proper dosing regimen of TXA in paediatric population is scarce. This trial was designed to determine the effectiveness of high dose TXA over low dose TXA in adolescent idiopathic scoliosis surgery to reduce surgical blood loss and allogenic transfusion requirement.

Methods: This prospective randomised double-blinded trial involved 166 patients with adolescents idiopathic scoliosis in University Malaya Medical Centre (UMMC) who were randomised to receive either Group A, high dose TXA (30 mg/kg loading dose and 10 mg/kg/h infusion) or Group B, low dose TXA (10 mg/kg loading dose and 1 mg/kg/h). Haemoglobin, haematocrit and fibrinogen levels were obtained at 3 perioperative time frames; T1 (preoperation), T2 (0-hour postoperation), and T3 (48-hour postoperation) which was then analysed using repeated measure analysis of variance (ANOVA) to detect the difference over time.

Results: The total surgical blood loss was insignificantly different ($p = 0.865$). Each group has one patient received perioperative allogenic blood transfusion. The main predictors contributing to the amount of surgical blood loss are number of vertebral level fused, duration of surgery and gender ($R^2 = 0.492$). The perioperative drop in haemoglobin levels between T1 and T3 for Group A and Group B (mean difference [95% confidence interval], 3.01 [2.60,3.42] versus 3.30 [2.89,3.71]) showed no significant difference ($p = 0.511$). No serious complications occurred in both groups.

Conclusions: Low dose TXA is as effective as high dose TXA in reduction of surgical blood loss and transfusion requirement in paediatric scoliosis surgery.

Keywords

Tranexamic acid, adolescent idiopathic scoliosis, blood loss, allogenic blood transfusion

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**ASID TRANESEMIK DALAM PEMBEDAHAN SKOLIOSIS PEDIATRIK
(TRIPSS):
KAJIAN RAWAK TERKAWAL MEMBANDINGKAN ASID TRANESEMIK
DOS TINGGI DAN DOS RENDAH UNTUK IDIOPATIK SKOLIOSIS REMAJA
YANG MENJALANI GABUNGAN SPINAL POSTERIOR**

ABSTRAK

Latar belakang: Asid Tranesamic (TXA) biasanya digunakan semasa pembedahan skoliosis bagi mengurangkan kadar pendarahan semasa pembedahan dan keperluan transfusi darah alogenik. Kajian mengenai rejimen dos TXA yang optimal masih terhad. Kajian ini dijalankan untuk menentukan keberkesanan TXA berdos tinggi berbanding TXA berdos rendah dalam pembedahan idiopatik skoliosis remaja untuk mengurangkan kadar pendarahan semasa pembedahan dan keperluan transfusi darah alogenik.

Kaedah: Ini merupakan kajian rawak terkawal yang melibatkan seramai 166 orang pesakit idiopatik skoliosis remaja di Pusat Perubatan Universiti Malaya (PPUM) dibahagikan kepada kumpulan A, TXA berdos tinggi (30 mg/kg dos pemuatan dan 10 mg/kg/jam infusi) atau kumpulan B, TXA berdos rendah (10 mg/kg dos pemuatan dan 1 mg/kg/jam infusi). Paras hemoglobin, hematokrit dan fibrinogen pada 3 tempoh masa perioperatif; T1 (sebelum pembedahan), T2 (0-jam selepas pembedahan) dan T3 (48-jam selepas pembedahan) yang kemudian dianalisa menggunakan analisis ukuran berulang varians (ANOVA) untuk mengesan perubahan dengan masa.

Keputusan: Jumlah pendarahan semasa pembedahan tidak menunjukkan perbezaan yang ketara ($p = 0.865$). Terdapat seorang pesakit di dalam setiap kumpulan yang memerlukan transfusi darah alogenik. Paras tulang vertebra yang disambung, jangka masa pembedahan dan jantina merupakan faktor utama yang menyumbang kepada jumlah pendarahan semasa pembedahan ($R^2 = 0.492$). Kadar penurunan paras hemoglobin perioperatif antara T1 dan T3 untuk kumpulan A dan kumpulan B (perbezaan min [95% selang keyakinan], 3.01 [2.60,3.42] lawan 3.30 [2.89,3.71])

menunjukkan tiada perbezaan ketara ($p = 0.511$). Tiada komplikasi serius yang dilaporkan bagi kedua-dua kumpulan.

Kesimpulan: TXA dos rendah mempunyai keberkesanan yang sama dengan TXA dos tinggi dalam mengurangkan pendarahan semasa pembedahan dan keperluan transfusi untuk pembedahan skoliosis pediatrik.

Kata kunci

Asid tranesamik, idiopatik skoliosis remaja, pendarahan, transfusi darah alogenik

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LIST OF SYMBOLS AND ABBREVIATIONS

| | |
|--------|--|
| AIS | Adolescent Idiopathic Scoliosis |
| ACD | Anticoagulant Citrate Dextrose |
| ACTRN | ANZ Clinical Trial Registration Number |
| ANOVA | Analysis of Variance |
| ANZCTR | Australian New Zealand Clinical Trial Registry |
| APTT | Activated Partial Thromboplastin Time |
| ASA | American Society of Anaesthesiologists |
| AUR | Acute Urinary Retention |
| BIS | Bispectral Index |
| EBL | Estimated blood loss |
| Et | End-tidal |
| Hb | Haemoglobin |
| Hct | Haematocrit |
| HR | Heart Rate |
| INR | International Normalised Ratio |
| IQR | Interquartile Range |
| IV | Intravenous |
| IVC | Inferior Vena Cava |
| MAC | Minimum Alveolar Concentration |
| MAP | Mean Arterial Pressure |
| PBM | Patient Blood Management |
| PSF | Posterior Spinal Fusion |
| PT | Prothrombin Time |
| SD | Standard Deviation |
| T1 | Pre-operation |

| | |
|-----|----------------------------|
| T2 | 0-hour post-operation |
| T3 | 48-hour post-operation |
| TCI | Target Controlled Infusion |
| TXA | Tranexamic Acid |
| g | gram |
| µg | microgram |
| mg | milligram |
| kg | kilogram |
| l | litre |
| ml | millilitre |
| dl | decilitre |
| min | minute |
| sec | second |
| IU | International Unit |

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CHAPTER 1: INTRODUCTION

Scoliosis surgery is the commonest and the most extensive procedure performed in paediatric population. Multilevel spine fusion and reconstruction are usually complicated by significant intraoperative blood loss and the requirement for allogenic blood transfusion (Sethna et al, 2005 & Wong et al, 2008). It has been reported that intraoperative blood loss is an important determinant for surgical outcome and recovery (Ersen et al, 2012).

Numerous interventions have been applied to reduce perioperative blood loss. The use of pharmacological agent to reduce surgical blood loss has remained to be one of the important strategies for perioperative Patient Blood Management (PBM). Administration of antifibrinolytics intraoperatively with the aim to reduce blood loss has gained popularity since 1990s (Florentino-Pineda et al, 2001). In the paediatric orthopaedic literature, Tranexamic Acid (TXA) has been shown to reduce blood loss and transfusion needs in posterior spinal fusion.

Various range of doses were applied, the lowest starting from loading dose of 10 mg/kg continued with maintenance 1mg/kg/hour to the highest loading dose of 100 mg/kg followed by maintenance 10mg/kg/hour. Several studies in cardiac surgery described the pharmacokinetic modelling of clinically efficacious TXA dosing in adults who reports the dosing schedules needed to maintain plasma levels of 52.5 and 126 µg/ml (Horrow et al, 1995 & Dowd et al, 2002), and recent studies suggested that plasma levels up to 150 µg/ml may be more effective and safe in adults with severe bleeding (Grassin-Delyle et al, 2013 & Sigaut et al, 2014).

Yee et al. (2013) elicited that TXA inhibits fibrinolysis at a minimum plasma level of 6.54 µg/ml in neonates, and 17.5 µg/ml in adults. In order to maintain an effective plasma concentration for TXA, we quote the reference value of 13-31 mg/kg loading dose followed by 5.5-14 mg/kg/hour infusion to maintain an intermediate to high

plasma level of 60-150 µg/ml in children aged above 12 months and above 20 kg going for cardiac surgery cardiopulmonary bypass (Wesley et al, 2015).

Nonetheless, limited number of pharmacokinetic modelling study in paediatric scoliosis surgery to ascertain the optimal dose to achieve adequate inhibition of fibrinolysis, as well as to dose which related to complications such as seizure and thromboembolic event.

The primary aim of this study was to determine the efficacy of high dose versus low dose TXA in reducing blood loss and transfusion requirement in paediatric scoliosis surgery. Secondary aim was to determine perioperative changes in haemoglobin level and coagulation profile in these two treatment groups and to report any adverse events or complication following TXA administration.

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CHAPTER 2: LITERATURE REVIEW

Bleeding is a known surgical complication. The magnitude of bleeding varies depending on the complexity of the surgical procedures. Excessive perioperative bleeding remains an important issue for the surgeons and the anaesthetist, as it is associated with increased morbidity, mortality and prolonged intensive care stay (de Boer et al, 2007).

Spine surgery particularly multilevel spine fusion and reconstruction are usually complicated by significant intraoperative blood loss and the requirement for allogenic blood transfusion (Neilipovitz et al, 2001). It has been reported that intraoperative blood loss is an important determinant for surgical outcome and recovery (Acebal-Cortina et al, 2011 & Chou et al, 2009).

A significant blood loss results in greater fluid shift which interrupts the stability of cardiopulmonary and renal system, and may cause imbalance of the haemostasis (Popovsky et al, 2001). This will increase the likelihood of transfusion with greater exposure to blood products and the potential for transfusion related problems including infection. There is also emerging data to suggest that blood products may harm the immune system and may be associated with an increased risk of infections which can be devastating (Carson et al, 1999 & Triulzi et al, 1992).

Spine surgery for correction of scoliosis is the commonest and then most extensive procedure performed in paediatric population. Children with scoliosis majority had a surgery done in the second decade of life. The underlying disorder plays a major role in determining the extent of intraoperative blood loss.

Bleeding is higher in children with neuromuscular scoliosis compared with idiopathic scoliosis with mean estimated blood loss ranging between 2000 – 3000 ml and 750 – 1000 ml respectively (Shapiro et al, 2004).

Blood loss is also shown to be proportionally greater with increasing numbers of vertebral levels involved into the fusion and with posterior fusions compared to anterior fusion (Hu SS, 2004 & Zheng et al, 2002). Although paediatric patients generally have lower blood loss during spinal procedures, a few millilitres of blood loss could have significant outcome and may lead to devastating neurological complications (Triulzi et al, 1992).

Numerous techniques have been described to minimise perioperative blood loss and allogenic blood transfusion during spine surgery. Reducing the rate of blood loss, salvaging the lost blood, and decreasing the requirement for transfusion are the possible area of intervention. Acute normovolemic hemodilution and autologous blood donation have been used to reduce the need of allogenic blood transfusion, thus reducing the risk of transmission of blood-borne infection. Alternatively, red blood cell salvage machine can be used to salvage the lost blood.

On the other hand, various methods have been implicated to reduce perioperative blood loss. Proper patient positioning is the first step to prevent pressure on inferior vena cava (IVC) which can lead to engorgement of epidural veins thus increase the rate of bleeding. Fast and efficient surgery should not be overlooked. With the advancement of current surgical techniques, the use of electrocautery and haemostatic agents will promote platelet aggregation and formation of blood clot, hence, reducing bleeding.

Administration of antifibrinolytics to reduce the rate of blood loss, such as aprotinin, epsilon-aminocaproic acid and tranexamic acid, has become the highlight and analysed well since 1990s (Ho et al, 2003 & Thompson et al, 2008). Tranexamic acid (TXA) is a synthetic lysine analogue that results in formation of a reversible complex with plasminogen which inhibits fibrinolysis. TXA is shown to be as effective as other antifibrinolytics but at much lower cost and lesser side effects. Extensive studies have

been conducted worldwide in attempts to evaluate its efficacy for controlling perioperative bleeding in major surgery including spine surgery.

TXA has been shown to reduce blood loss and transfusion requirements in posterior spinal fusion for both neuromuscular as well as idiopathic scoliosis. The efficacy of TXA has been postulated to be dose dependent but no consensus has been reached on the most appropriate dosing regimen. TXA dose up to 100 mg/kg have been recommended (Farrokhi et al, 2011). However, a significant increase in clinical seizures with no increase in thromboembolic effects in the early postoperative period was noted in 2 institutions after introduction of routine TXA infusion for high risk cardiac surgical patients.

The plasma half-life of TXA is relatively short (2-3 hours) and its effect cannot be guaranteed throughout the 24-hour period subsequent to the surgical procedures. Thus, continuous infusion is crucial after a loading dose to maintain the plasma level of TXA throughout the surgery. Mosaad et al (2017) reported that both high dose (50 mg/kg bolus followed by 20 mg/kg/hour) and low dose (10 mg/kg bolus followed by 1mg/kg/hour) groups had a significantly less blood loss and higher postoperative haemoglobin levels than the control group. In another setting, lower dose of TXA have not achieved the same proportional reduction in perioperative bleeding (Grassin-Delyle, 2013).

CHAPTER 3: METHODOLOGY

3.1 Patient Subjects

A single tertiary centre randomised double blind (surgeons and patients) trial was performed between March 2017 and November 2018, after receiving approval from the Institutional Review Board. The protocol for this study was registered at the Australian New Zealand Clinical Trial Registry (ANZCTR), with registration number ACTRN12617000663358.

Patients aged 10 to 21 years old with adolescent idiopathic scoliosis (AIS) who were scheduled for elective single-level posterior spinal fusion (PSF) were evaluated. These patients were then recruited when they were American Society of Anaesthesiologists (ASA) physical status I and II, with preoperative haemoglobin > 10 g/dl and preoperative platelet count $> 150,000/u/l$. Exclusion criteria were severe haematological disorder, severe cardiac disease, patients who received anticoagulants and antiplatelet within 14 days prior to operation, severe restrictive pulmonary disease, and patients with preoperative serum creatinine > 200 mmol/l and serum aspartate aminotransferase > 100 IU/l.

Patients were randomly assigned to either one Tranexamic Acid (TXA) treatment groups, which was Group A or Group B, using concealed allocation method. A computerised random number generator was used to formulate an allocation schedule. Group A received a loading of 30 mg/kg TXA, followed by 10 mg/kg/hour of maintenance dose, whereas Group B was given a loading dose of 10 mg/kg followed by a maintenance dose of 1mg/kg/hour, designated as high and low dosing respectively.

Allocation was revealed prior to surgery from a sealed envelope containing the allocation (labelled as Group A or B). The medications were prepared before induction by the investigator and held to the anaesthetist in charge for administration following the study protocol.

3.2 Anaesthetic Technique

All patients were adequately fasted for at least 6 hours prior to surgery. Induction of anaesthesia was carried out with intravenous (IV) Propofol 2-4 mg/kg, single dose IV Rocuronium 1.0 mg/kg and Target Controlled Infusion (TCI) of Remifentanyl 1-5 ng/ml to facilitate endotracheal intubation. Patients were ventilated with 50% Oxygen/air mixture. The anaesthesia was maintained with balanced anaesthesia technique using volatile anaesthetic Desflurane with minimum alveolar concentration (MAC) of 0.6-0.8 (EtDesflurane of 5.0), TCI Remifentanyl between 2-5 ng/ml, and IV rocuronium 5 mg intermittent bolus. IV Tranexamic Acid was given to the patients according to the allocation.

Bispectral index monitor (BIS) is used to monitor depth of anaesthesia with a target BIS of 40-60. Continuous monitoring of patients was carried out using invasive blood pressure via radial artery cannulation, heart rate (HR), pulse oximetry and 3-lead electrocardiogram. Intraoperative cell salvage is used in all the patients irrespective of allocation group and was operated by a trained perfusionist.

Hartmann solution was used intraoperatively as maintenance fluid therapy and as replacement for intraoperative insensible fluid losses in accordance to Holliday-Segar formula. Additional 5 ml/kg bolus of crystalloid would be given when mean arterial pressure (MAP) decreases below 60 mmHg, heart rate (HR) increases by 20% from baseline, and urine output of less than 0.5 ml/kg/hour. Crystalloid bolus can be repeated up to 4 times if necessary.

Immediate cell salvage blood was returned when there was more than 20% loss of blood volume, or else the collected blood is reinfused at the completion of the surgery. Allogenic blood transfusion was initiated when haemoglobin level < 8 g/dl despite completion of cell salvage blood reinfusion and adequate fluid resuscitation with persistent hemodynamic instability (persistent hypotension or tachycardia >20% from

baseline). The algorithm for intraoperative fluid management for this trial as illustrated in Appendix A.

3.3 Surgical Protocol and Assessment of Blood Volume Loss

The surgical protocol for all patients was similar. All cases were operated by two same senior surgeons. Postoperative drainage was managed using the following protocol. Immediately after completion of the operation, the suction was clamped. At 18-24 hours postoperative period, the drain would then be removed after draining a maximum of 200 ml of blood.

Baseline characteristics of patients such as age, gender, height, weight, body blood volume (estimated using Nadler's formula), and baseline operative details such as number of vertebral level fused, Cobb's angle, number of screws used, duration of surgery, and skin incision length were recorded.

Total intraoperative blood loss is calculated from the cell salvage system as well as by weighing the soaked sponges. Blood loss from the floor, surgical gowns, and drapes were not included. Estimation of total blood loss by the cell salvage system is calculated using the following formula:

- Total intraoperative blood loss (ml) = (Final volume accumulated in the reservoir – Total volume of Anticoagulant Citrate Dextrose (ACD) – Total irrigation fluid used intraoperative) + Total unfiltered blood + Total soaked sponges
- Total surgical blood loss (ml) = Total intraoperative blood loss + Total blood collected in the surgical drain postoperatively until drain removal

Patients with postoperative haemoglobin value of less than 8g/dl will receive one unit of allogenic packed red cell transfusion. Haemoglobin (Hb) change was assessed by means of laboratory test over the following time set-points: (T1): pre-operation; (T2):

post-operation 0 hour; (T3): post-operation 48 hour. All patients were followed up until hospital discharge and within 30 days post operation period.

3.4 Statistical Analysis

We used power study was performed using web based sample size calculator to determine our sample size. Our main outcome variable was total surgical blood loss (ml) measured in continuous scale and our main objective was to compare among two treatment groups (high dose versus low dose).

We retrieved the information of estimated blood loss, EBL (ml) from previous published article and found that the amount of EBL (ml) for low dose group was 968 ± 756 mL and high dose group was 695 ± 372 ml (Johnson et al, 2016). We set the type 1 error probability as 0.05 and power of 0.8. Hence, the required sample size was 69 per group. To add on a 20% dropout rate at 30 days of follow-up (Tushar, 2010), the final calculated sample size was 76.67 subjects/arm. Therefore, the total sample size enrolled into this study was 160 patients.

All data were analysed using SPSS software version 23. Variables were expressed as mean \pm standard deviation (SD) and compared with the parametric independent sample t-test. Data with skewed distribution were compared with the Mann-Whitney U test and expressed as median (interquartile range). Categorical data were presented as frequencies (percentages) and compared with the χ^2 test. Level of significance is set at $p < 0.05$.

Bivariate correlation analysis and simple linear regression were used to identify variables that influenced the total surgical blood loss. The independent variables were number of vertebral level fused, Cobb's angle, number of screws used, duration of surgery and skin incision length. One way repeated measures analysis of variance (ANOVA) was used to obtain the profile plots to demonstrate serial blood counts and coagulation profile at different time which includes haemoglobin (Hb) level,

haematocrit (Hct) level, platelet counts, prothrombin time (PT), international normalised ratio (INR), activated partial thromboplastin time (APTT) and fibrinogen level.

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CHAPTER 4: RESULTS

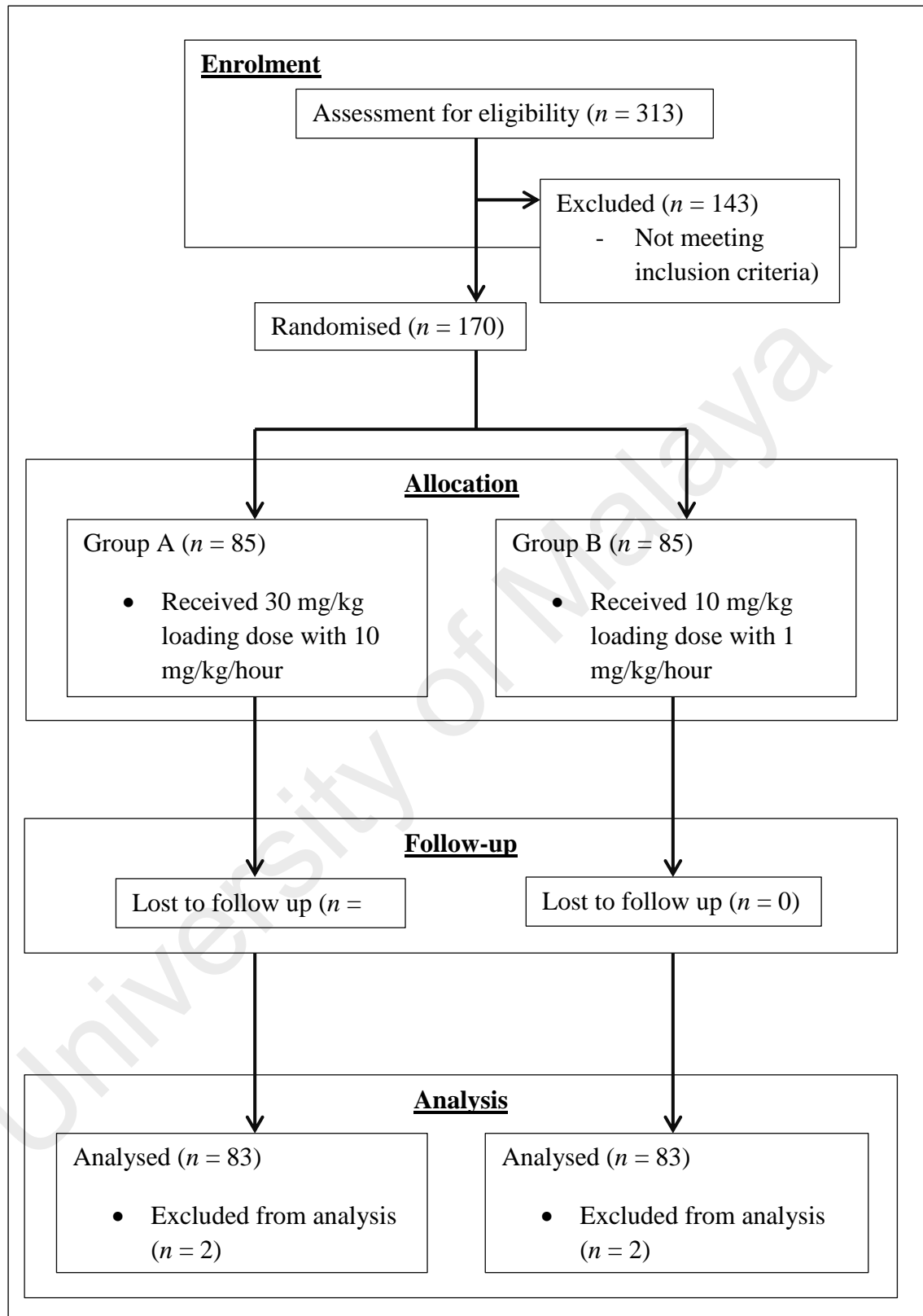


Figure 1: CONSORT (Consolidated Standards of Reporting Trials) diagram.

Figure 1 illustrated the patient flow in this study. A total of 313 patients were planned for scoliosis surgery from March 2017 until November 2018. One-hundred and forty three patients were excluded from recruitment following the exclusion criteria, mainly because of the age limit. Participants then were randomly assigned to two treatment groups. At the end of the study, two participants from each group were excluded from analysis due to cancellation of surgery and breach of the study protocol.

Patients' demographics for both treatment groups are presented in Table 1. Mean age for both groups was 14 years and majority were female (> 60%). The starting haemoglobin level was 13 g/dl for both treatment groups. The average Cobb's angle was 67 degree and 65 degree for group A and group B respectively as shown in Table 2. Both group A and B had median of 14 screws inserted during the corrective surgery.

Table 1: Demographic details and preoperative laboratory and hemodynamic data for high dose versus low dose TXA group

| Variables | Treatment Group | | Whole Group | p value |
|------------------------------------|------------------------|-----------------------|----------------|---------|
| | A (High dose), n=83 | B (Low dose), n=83 | | |
| Demographics | | | | |
| Age, years (Mean±SD) | 14.14±2.14 | 14.60±3.00 | 14.37±2.60 | 0.259 |
| Gender, n (%) | | | | 0.067 |
| Male | 7 (31.8) | 15 (68.2) | 22 (13.3) | |
| Female | 76 (52.8) | 68 (47.2) | 144 (86.7) | |
| Weight, kg (Mean±SD) | 45.29±9.04 | 46.58±9.31 | 45.93±9.17 | 0.366 |
| Height, cm (Mean±SD) | 156.72±6.45 | 157.11±7.92 | 156.92±7.20 | 0.730 |
| Body blood volume, ml (Mean±SD) | 3072.87±497.16 | 3202.29±582.14 | 3137.58±543.57 | 0.125 |

SD: standard deviation

‘Table 1 continued’

| Baseline laboratory data | | | | |
|---|--------------|--------------|--------------|-------|
| Hemoglobin, g/dL (Mean±SD) | 13.73±0.99 | 13.84±1.12 | 13.78±1.05 | 0.483 |
| Hematocrit, % (Mean±SD) | 0.42±0.03 | 0.42±0.03 | 0.42±0.31 | 0.682 |
| Platelet, x10 ³ u/L (Mean±SD) | 305.20±54.43 | 314.04±65.94 | 309.54±60.33 | 0.353 |
| PT, sec (Mean±SD) | 11.34±0.71 | 11.48±0.74 | 11.41±0.72 | 0.236 |
| INR (Mean±SD) | 1.05±0.07 | 1.06±0.06 | 1.06±0.07 | 0.291 |
| APTT (Mean±SD) | 34.68±4.84 | 35.46±3.73 | 35.07±4.32 | 0.265 |
| Fibrinogen (Mean±SD) | 2.82±0.62 | 2.74±0.53 | 2.78±0.58 | 0.435 |
| Baseline hemodynamic data | | | | |
| HR, beats/min (Mean±SD) | 78.43±12.03 | 79.25±12.90 | 78.86±12.46 | 0.685 |
| MAP, mmHg (Mean±SD) | 70.00±6.58 | 69.87±7.33 | 69.93±6.96 | 0.911 |

SD: standard deviation; PT: prothrombin time; INR: international normalised ratio; APTT: activated partial thromboplastin time; HR: heart rate; MAP: mean arterial pressure.

Table 2: Operative details for high dose versus low dose TXA group

| Variables | Treatment Group | | Whole Group | p value |
|---------------------------------------|------------------------|-----------------------|--------------------|----------------|
| | A (High dose), n=83 | B (Low dose), n=83 | | |
| Operative Details | | | | |
| Vertebral level fused, n (Mean±SD) | 11.37±2.16 | 10.88±2.03 | 11.13±2.10 | 0.131 |
| Cobb’s angle, degree (Mean±SD) | 67.70±16.86 | 65.82±13.75 | 66.76±15.37 | 0.432 |
| Screws fused, n (Median±IQR) | 14±4 | 14±3 | 14±3 | 0.299 |

SD: standard deviation

‘Table 2 continued’

| | | | | |
|--|---------------------|---------------------|---------------------|--------------|
| Duration of surgery, min (Mean±SD) | 131.86±38.53 | 126.67±38.65 | 129.27±38.56 | 0.388 |
| Skin incision length, cm (Mean±SD) | 30.23±5.60 | 29.42±5.44 | 29.83±5.51 | 0.347 |
| Length of hospital stay, day (Mean±SD) | 3.05±0.58 | 3.08±0.74 | 3.07±0.66 | 0.726 |

SD: standard deviation; IQR: interquartile range.

The intraoperative fluid management and perioperative blood details were as summarised in Table 3. The mean intraoperative blood loss was 830 ml but the difference between these two groups was insignificant. However, high dose TXA group has significantly lower volume of gauze blood ($p < 0.001$) and post-operative 24-hour drain volume ($p = 0.03$) as compared to low dose TXA group. Nonetheless, both groups have a subject receiving allogenic blood transfusion during perioperative period.

Table 3: Intraoperative fluid requirement and perioperative blood management for high dose versus low dose TXA group

| Variables | Treatment Group | | Whole Group | p value |
|---|------------------------|-----------------------|----------------|---------|
| | A (High dose), n=83 | B (Low dose), n=83 | | |
| Intraoperative fluid and vasopressor requirement | | | | |
| Total crystalloid | | | | |
| ml (Mean±SD) | 1243.13±303.67 | 1247.59±325.25 | 1245.36±313.70 | 0.927 |
| ml/kg (Mean±SD) | 28.11±7.71 | 27.72±8.73 | 27.92±8.21 | 0.766 |
| Total colloid | | | | |
| ml (Mean±SD) | 33.13±133.95 | 66.27±183.65 | 49.70±161.10 | 0.186 |
| ml/kg (Mean±SD) | 0.85±3.50 | 1.67±5.04 | 1.26±4.35 | 0.222 |

SD: standard deviation;

‘Table 3 continued’

| | | | | |
|--|----------------|----------------|----------------|--------|
| Total fluid infused | | | | |
| ml (Mean±SD) | 1276.27±320.94 | 1313.86±412.70 | 1295.06±369.04 | 0.513 |
| ml/kg (Median±IQR) | 28.33±10.41 | 26.18±13.22 | 27.06±11.35 | 0.497 |
| Total ephedrine used, mg (Mean±SD) | 0.51±2.52 | 1.08±3.91 | 0.80±3.29 | 0.259 |
| Total phenylephrine used, mcg (Mean±SD) | 14.46±70.07 | 22.89±105.14 | 18.67±89.18 | 0.544 |
| Total urine output, ml (Median±IQR) | 140±125 | 100±205 | 120±165 | 0.092 |
| Perioperative blood management | | | | |
| Cell salvage blood return, ml (Mean±SD) | 442.69±235.64 | 419.95±222.40 | 431.32±228.71 | 0.524 |
| Volume of gauze blood, ml (Median±IQR) | 14±16 | 20±18 | 17±16 | <0.001 |
| Intraoperative blood loss | | | | |
| ml (Mean±SD) | 844.93±384.89 | 815.13±383.86 | 830.03±383.50 | 0.618 |
| ml/level (Mean±SD) | 73.70±29.23 | 73.49±29.24 | 73.59±29.14 | 0.964 |
| ml/hour (Mean±SD) | 385.36±141.19 | 388.40±150.47 | 386.88±145.47 | 0.893 |
| Postoperative 24h drain volume, ml (Mean±SD) | 83.92±55.45 | 103.01±58.12 | 93.46±57.93 | 0.032 |
| Surgical blood loss | | | | |
| ml (Mean±SD) | 928.84±406.12 | 918.14±406.22 | 923.49±404.97 | 0.865 |
| ml/level (Mean±SD) | 80.87±30.12 | 82.84±30.46 | 81.86±30.21 | 0.676 |

SD: standard deviation; IQR: interquartile range.

‘Table 3 continued’

| | | | | |
|--|---------|---------|------------|-------|
| Perioperative allogenic transfusion, n (%) | | | | 0.497 |
| No | 82 (50) | 82 (50) | 164 (98.8) | |
| Yes | 1 (50) | 1 (50) | 2 (1.2) | |

Table 4: Adverse events and complications during perioperative and 30 days post-operative period

| Complication | Group A, n (%) | | Group B, n (%) | |
|---|----------------|------------|----------------|------------|
| | In hospital | At 30 days | In hospital | At 30 days |
| Allergic / Anaphylaxis reaction | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| Infection | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| Haemorrhage | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| Cardiac complication | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| Cerebrovascular / Cerebral complication | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| Vascular / Thromboembolism | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| Respiratory complication | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| Gastrointestinal complication | 3 (3.6) | 0 (0) | 2 (2.9) | 0 (0) |
| Nausea/vomiting | 2 (2.4) | 0 (0) | 1 (1.2) | 0 (0) |
| Ileus | 1 (1.2) | 0 (0) | 1 (1.2) | 0 (0) |
| Renal / Urinary complication | 1 (1.2) | 0 (0) | 0 (0) | 0 (0) |
| AUR | 1 (1.2) | 0 (0) | 0 (0) | 0 (0) |
| Others | 0 (0) | 0 (0) | 0 (0) | 0 (0) |

AUR: acute urinary retention

No serious adverse events observed for both treatment groups during perioperative up to 30 days post-operative period (Table 4). The commonest discomfort experience during immediate post-operation was gastrointestinal related symptoms like nausea and vomiting possibly related to opioid usage. One patient in high dose TXA group had acute urinary retention which resolved at day 2 post-operation. No thromboembolic event or seizure reported throughout this study.

Table 5: Surgical factors affecting surgical blood loss in idiopathic scoliosis surgery

| Factors | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
|-------------------------------------|--------|--------|--------|--------|--------|--------|---------|
| 1. Surgical blood loss [‡] | 0.580* | 0.376* | 0.430* | 0.611* | 0.520* | -0.013 | -0.252* |
| 2. Vertebral level fused | - | 0.501* | 0.665* | 0.554* | 0.842* | -0.118 | -0.044 |
| 3. Cobb angle | | - | 0.364* | 0.345* | 0.381* | -0.061 | 0.017 |
| 4. Screws used | | | - | 0.554* | 0.596* | -0.111 | -0.033 |
| 5. Duration of surgery | | | | - | 0.511* | -0.067 | -0.130 |
| 6. Skin incision length | | | | | - | -0.073 | -0.158* |
| 7. Dose of TXA | | | | | | - | -0.142 |
| 8. Gender | | | | | | | - |

*p < 0.05; ‡ There is a weak correlation between length of hospital stay and surgical blood loss (r = 0.242, p = 0.002)

Based on Table 5, surgical blood loss has moderate correlation ($0.4 \leq r \leq 0.69$, $p < 0.05$) with number of vertebral level fused, number of screw used, duration of surgery and skin incision length. Cobb angle has weak association with the amount of intraoperative blood loss ($r \leq 0.3$, $p < 0.05$). On the other hand, weak negative association ($r \leq 0.3$, $p < 0.05$) was found between gender and surgical blood loss. Dosage of TXA has insignificant correlation with surgical blood loss ($p = 0.865$).

Table 6: Significant Independent Multivariable Predictors of Surgical Blood Loss[†]

| Predictors | Standard | | | |
|-----------------------|---------------|--------|---------|---------|
| | B ± SE | β | T value | p value |
| Vertebral level fused | 67.13±13.34 | 0.349 | 5.03 | <0.001 |
| Duration of surgery | 4.39±0.73 | 0.418 | 6.03 | <0.001 |
| Gender | -220.79±67.32 | -0.185 | -3.28 | 0.001 |

R² = 0.492

[†]Multivariable linear regression analysis adjusted for Cobb angle, number of screw used, skin incision length and dosage of TXA (all not significant, p>0.50)

Further multivariable linear regression analysis that included 7 independent factors – number of vertebral level fused, Cobb angle, number of screw used, duration of surgery, skin incision length, gender and dosage of TXA as shown in Table 6. Only number of vertebral level fused (p<0.001), duration of surgery (p<0.001) and gender (p = 0.001) significantly predict surgical blood loss. Surgical blood loss is increased by 67ml for each vertebral level fused and increased by 4ml for additional minute of surgical time. Female gender has reduced surgical blood loss by 220 ml as compared to male.

Table 7: Mean laboratory data for high dose versus low dose TXA group

| Laboratory Data | Group A (High dose) | Group B (Low dose) | p-value |
|-------------------------|---------------------|--------------------|---------|
| | Mean±SD | Mean±SD | |
| Hemoglobin, g/dl | | | |
| T1 | 13.76 ± 0.97 | 13.84 ± 1.11 | 0.483 |
| T2 | 11.91 ± 1.17 | 11.72 ± 1.22 | 0.861 |
| T3 | 10.75 ± 1.29 | 10.54 ± 1.09 | 0.256 |

SD: standard deviation

'Table 7 continued'

| Hematocrit, % | | | |
|---|--------------|--------------|-------|
| T1 | 0.42±0.30 | 0.42±0.32 | 0.682 |
| T2 | 0.36±0.04 | 0.36±0.04 | 0.993 |
| T3 | 0.33±0.41 | 0.32±0.03 | 0.265 |
| Platelet count, x10³u/l | | | |
| T1 | 305.20±54.43 | 314.04±65.94 | 0.353 |
| T2 | 248.88±49.49 | 248.27±65.50 | 0.947 |
| T3 | 211.10±56.42 | 208.39±51.36 | 0.779 |
| PT, sec | | | |
| T1 | 11.34±0.71 | 11.48±0.74 | 0.236 |
| T2 | 13.08±0.90 | 13.44±2.10 | 0.158 |
| T3 | 13.48±1.39 | 13.34±1.42 | 0.583 |
| INR | | | |
| T1 | 1.05±0.73 | 1.06±0.06 | 0.291 |
| T2 | 1.21±0.09 | 1.25±0.19 | 0.094 |
| T3 | 1.25±0.14 | 1.23±0.13 | 0.568 |
| APTT, sec | | | |
| T1 | 34.68±4.84 | 35.46±3.73 | 0.265 |
| T2 | 40.93±26.75 | 42.57±27.61 | 0.704 |
| T3 | 31.88±3.40 | 31.78±3.18 | 0.869 |
| Fibrinogen, g/l | | | |
| T1 | 2.82±0.62 | 2.74±0.53 | 0.435 |
| T2 | 2.08±0.69 | 2.05±0.42 | 0.740 |
| T3 | 5.35±1.39 | 5.00±0.98 | 0.116 |

SD: standard deviation; PT: prothrombin time; INR: International Normalised Ratio; APTT: activated partial thromboplastin time; T1: Pre-operation; T2: 0-hour post-operation; T3: 48-hour post-operation

Table 8: Mean difference of the laboratory data over time for high dose versus low dose TXA group

| | Group A (High dose) | | | Group B (Low dose) | | |
|-------------------------------------|---------------------|----------------|----------------|--------------------|----------------|----------------|
| | Mean difference | 95% CI | <i>p</i> value | Mean difference | 95% CI | <i>p</i> value |
| Hemoglobin, g/dl † | | | | | | |
| T1 vs T2 | 1.84 | (1.54,2.15) | <0.001 | 2.12 | (1.81,2.43) | <0.001 |
| T1 vs T3 | 3.01 | (2.60,3.42) | <0.001 | 3.30 | (2.89,3.71) | <0.001 |
| T2 vs T3 | 1.17 | (0.76,1.57) | <0.001 | 1.18 | (0.82,1.54) | <0.001 |
| Hematocrit, % | | | | | | |
| T1 vs T2 | 0.07 | (0.05,0.08) | <0.001 | 0.07 | (0.06,0.08) | <0.001 |
| T1 vs T3 | 0.09 | (0.08,0.11) | <0.001 | 0.10 | (0.09,0.11) | <0.001 |
| T2 vs T3 | 0.03 | (0.01,0.04) | <0.001 | 0.03 | (0.02,0.04) | <0.001 |
| Platelet, x10³u/l | | | | | | |
| T1 vs T2 | 56.49 | (43.78,69.19) | <0.001 | 69.58 | (52.71,86.45) | <0.001 |
| T1 vs T3 | 92.34 | (76.96,107.72) | <0.001 | 101.48 | (87.29,115.68) | <0.001 |
| T2 vs T3 | 35.85 | (23.79,47.92) | <0.001 | 31.90 | (16.54,47.26) | <0.001 |
| PT, sec | | | | | | |
| T1 vs T2 | -1.89 | (-2.14,-1.65) | <0.001 | -2.11 | (-2.79,-1.42) | <0.001 |
| T1 vs T3 | -2.21 | (-2.58,-1.84) | <0.001 | -1.84 | (-2.30,-1.38) | <0.001 |
| T2 vs T3 | -0.32 | (-0.70,0.07) | 0.14 | 0.27 | (-0.56,1.11) | >0.99 |
| INR | | | | | | |
| T1 vs T2 | -0.17 | (-0.19,-0.15) | <0.001 | -0.20 | (-0.26,-0.13) | <0.001 |
| T1 vs T3 | -0.20 | (-0.24,-0.17) | <0.001 | -0.17 | (-0.21,-0.13) | <0.001 |
| T2 vs T3 | -0.03 | (-0.07,0.004) | 0.100 | 0.03 | (-0.05,0.10) | >0.999 |

CI: confidence interval; PT: prothrombin time; INR: International Normalised Ratio; T1: Preoperation; T2: 0-hour postoperation; T3: 48-hour postoperation

‘Table 8 continued’

| APTT, sec | | | | | | |
|-------------------------------------|-------|---------------|--------|-------|---------------|--------|
| T1 vs T2 | -5.26 | (-12.14,1.61) | 0.193 | -5.41 | (-13.55,2.73) | 0.319 |
| T1 vs T3 | 2.61 | (1.14,4.08) | <0.001 | 3.92 | (2.86,4.99) | <0.001 |
| T2 vs T3 | 7.87 | (1.04,14.70) | 0.018 | 9.33 | (1.21,17.45) | 0.019 |
| Fibrinogen, g/l ^γ | | | | | | |
| T1 vs T2 | 0.80 | (0.53,1.07) | <0.001 | 0.79 | (0.64,0.93) | <0.001 |
| T1 vs T3 | -2.34 | (-2.70,-1.97) | <0.001 | -2.08 | (-2.45,-1.71) | <0.001 |
| T2 vs T3 | -3.14 | (-3.49,-2.79) | <0.001 | -2.87 | (-3.24,-2.49) | <0.001 |

CI: confidence interval; APTT: activated partial thromboplastin time; T1: Preoperation; T2: 0-hour postoperation; T3: 48-hour postoperation.

‡ Repeated measure ANOVA proceed and found no significant difference of 0.511 between the treatment group.

γ Repeated measure ANOVA proceed and found no significant difference of 0.269 between the treatment group.

The laboratory data at different time frames are illustrated in Table 7. There was significant different ($p < 0.001$) in total perioperative drop (T1 minus T3) in haemoglobin level across the 2 groups (Group A 3.01 g/dl, Group B 3.30 g/dl). Group A has a higher haemoglobin level as compared to group B at 0-hour and 48-hour post-operation. Similar pattern was seen for haematocrit level. Both group A and B showed a rise in fibrinogen level during postoperative period with higher level of rise in group A (2.34; $p < 0.001$) than group B (2.08; $p < 0.001$). Nonetheless, further analysis revealed insignificant difference of haemoglobin and fibrinogen level between two treatment groups.

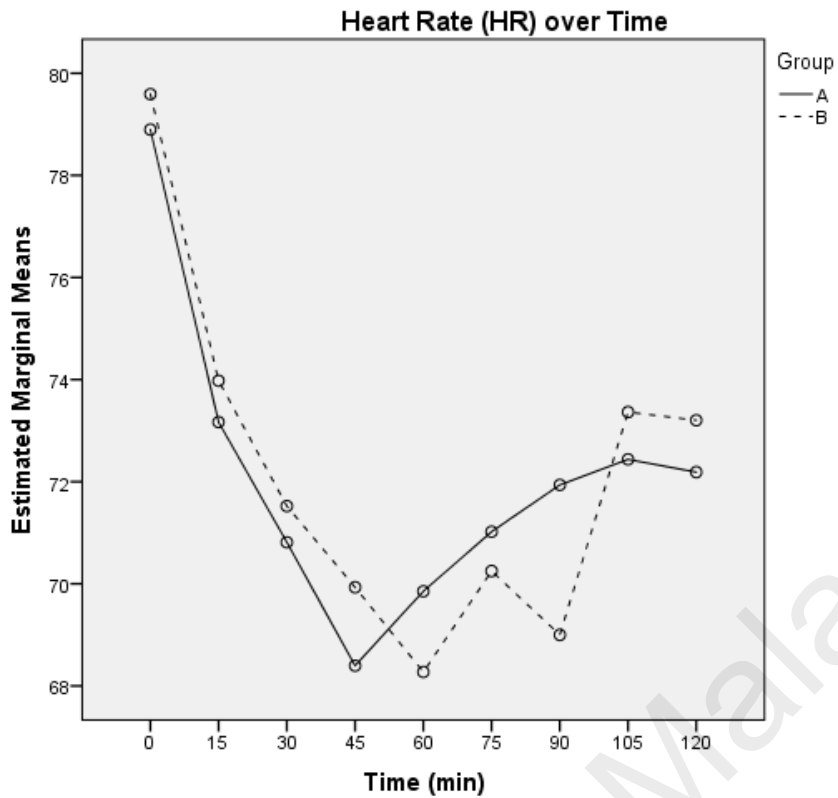


Figure 2.1: Serial means of heart rate at pre-operation (T1), 0-hour post-operation (T2) and 48-hour post-operation (T3)

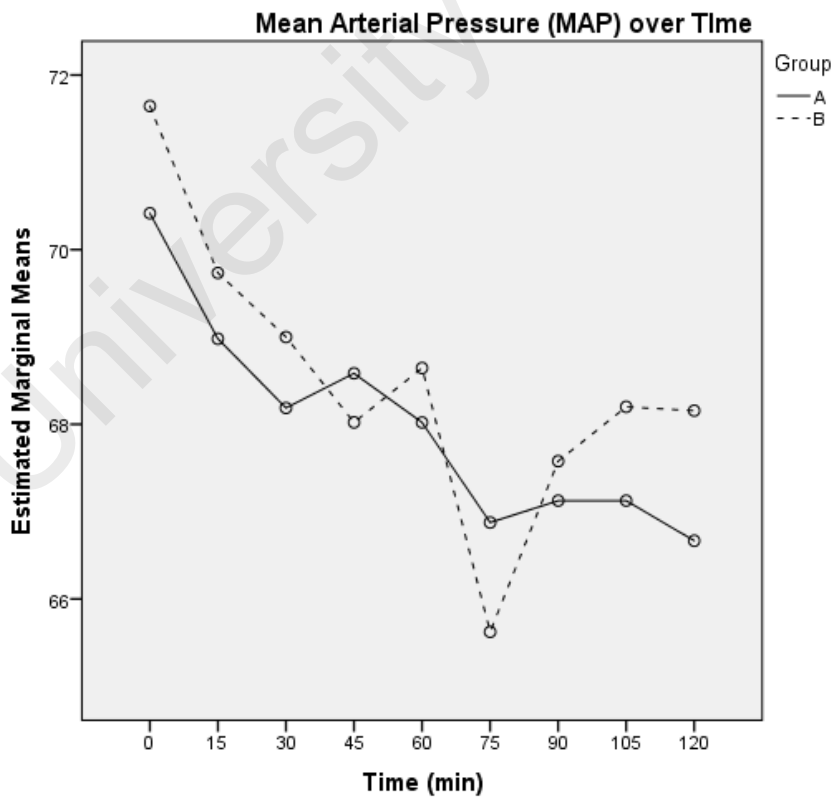


Figure 2.2: Serial means of mean arterial pressure (MAP) at pre-operation (T1), 0-hour post-operation (T2) and 48-hour post-operation (T3).

Figure 2.1 and Figure 2.2 demonstrate the serial means of intraoperative mean arterial pressure (MAP) and heart rate (HR) for both treatment groups. Group B has more fluctuation in intraoperative hemodynamic parameters especially towards the second hour of surgery with lowest MAP < 65mmHg. No significant tachycardia in response to the drop in MAP was observed due to concurrent use of TCI Remifentanyl throughout the surgery.

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CHAPTER 5: DISCUSSION

The complexity of scoliosis surgery increases the likelihood of bleeding during the perioperative period. The release of tissue factor, inflammatory mediators and the activation of the coagulation cascade will cause hyperfibrinolysis, hence increase surgical blood loss. Goobie et al. (2018) has demonstrated the efficacy of TXA in reducing cumulative blood loss by 27% and simultaneously reduce the need of blood transfusion. The percentage of allogenic blood transfusion required in this study was dispensable (1.2%).

Majority of the high level of evidence studies in spinal surgery are in favour with the use of TXA (Cheriyana et al, 2015 & Wong et al, 2008). However, the optimal dosing was still indefinite. This is due to the wide range of TXA dosing been utilised in patients with idiopathic scoliosis undergoing spinal fusion (Lykissas et al, 2013 and Verma et al, 2014). A systemic review and meta-analysis (Alajmi et al, 2017) showed high dose TXA is more effective than low dose TXA in reducing perioperative blood loss and transfusion requirement. Yet, some of the studies included in the analysis were underpowered with low sample size.

In our study, our high dose group received a loading dose of 30 mg/kg and a maintenance dose of 10 mg/kg/hour following a pharmacokinetic study in order to maintain a steady plasma level of TXA but the result was statistically insignificant. Similar outcome were obtained by McCormack PL (2012), Dunn & Goa (1999) and Neilipovitz et al (2001), whereby a significant reduction of blood loss and blood transfusion were reported even at lower dose. Ker et al (2012) and Yang et al (2013) reported that higher doses TXA only provide little additional hemostatic benefit.

High dose of TXA raise a great concern regarding toxicity. High dose TXA is associated with postoperative convulsive seizure in cardiac surgery (Murkin et al, 2010 and Manji et al, 2012). Wang et al (2011) reported that TXA was an independent

predictor of postoperative seizures. It penetrates the blood brain barrier and 10% of TXA plasma concentration was found in the cerebrospinal fluid and aqueous humour. Nevertheless, none of our patients had seizure up to 30 days follow up even when it is administered in a patient with normal pressure hydrocephalus.

Higher postoperative fibrinogen level was observed with the administration of antifibrinolytic agents (Thompson et al, 2007), raising the concern of thromboembolic events. In our study, the high dose group has higher postoperative fibrinogen level than low dose group. Yet this result was not statistically significant and it was not powered to make any conclusions on safety. Neilipovitz et al. (2001) evaluated the risks in a randomised-control trial with no cases of clinical thrombotic events or hemodynamic instability. Another study in scoliosis surgery detecting no clinical evidence of deep vein thrombosis during postoperative period (Sethna et al, 2005) supporting our finding. Ialenti et al. (2013) and Berney et al. (2015) reported that prolonged operative time is associated with increased blood loss, hence leading to lower postoperative haemoglobin level and increase transfusion requirement. However, several studies reported negative results regarding hematologic profiles (Peters et al, 2015). There was no difference in haemoglobin levels between the two treatment groups in our study.

A recent retrospective study among patients undergoing elective spinal surgery found an increased length of stay and postoperative morbidity in those who received transfusion (Seicean et al, 2014). Our patients had an average hospital stay of 3 days and there was no difference between high dose and low dose group. There was a weak association between surgical blood loss and the length of hospital stay in our study ($r < 0.4$).

A limitation of this study showed no significant difference between the rate of blood loss and transfusion requirement between high dose and low dose group. This can be due to our high dosing regime is comparably lower than the other study which used 50

mg/kg (Goobie et al, 2018 and Wang et al, 2013) and 100 mg/kg (Ng et al, 2015 & Lykissas et al, 2013). Hence, we are unable to support the fact that TXA effect is dose dependent. A pharmacokinetic study should be performed to determine the effective safe dosing of TXA in paediatric scoliosis surgery.

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CHAPTER 6: CONCLUSION

High dose TXA showed no superiority than low dose TXA in perioperative reduction of blood loss and transfusion requirement in paediatric scoliosis surgery. Both high dose and low dose TXA has similar decreased in haemoglobin levels between preoperative values and at 48 hour postoperative.

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