International Orthopaedics (2022) 46:1721–1729
https://doi.org/10.1007/s00264-022-05416-y

ORIGINAL PAPER

Is intravenous tranexamic acid effective in reduction of blood loss during pelvic and acetabular surgery?

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Received: 3 April 2022 / Accepted: 24 April 2022 / Published online: 7 May 2022

Abstract

Purpose Pelvic and acetabular surgery is associated with one of the highest amounts of blood loss. Tranexamic acid is a good choice to reduce blood loss during this type of surgery. However, being antifibrinolytic drug, the chance to have coagulation complications including DVT is a risk that should be considered particularly in such major trauma patients with the body's response to trauma and with possible prolonged bed stay. The aim of this study is to evaluate the effectiveness of intravenous tranexamic acid injection during pelvic and acetabular surgery for reduction of blood loss during surgery and after surgery and to evaluate any possible complications for its use.

Methods This prospective randomized clinical trial includes 97 patients divided between two groups; group 1 (G1) which received TXA, while the second group (G2) is the control group. The primary outcome measures were total blood loss (TBL), allogenic blood units transfused, and the blood lost intra-operatively (IBL). The TBL was calculated by the haemoglobin balance method while the intra-operative blood loss was measured by the gravimetric method. Any complications related to the drug were evaluated particularly DVT.

Results The study showed significantly less TBL ($G1 = 829.7 \pm 219.2$, $G2 = 1036.9 \pm 314.9$) and blood transfusion ($G1 = 52.4 \pm 40$ g, $G2 = 89.4 \pm 60.6$ g) in G1 compared to the G2.

Conclusion This study proved the possible reduction of TBL and the need of blood transfusion by the use of TXA in pelvic and acetabular injuries.

Keywords Tranexamic acid · Intravenous · Pelvic · Acetabular fractures · Blood loss · Blood transfusion

Introduction

Tranexamic acid is an antifibrinolytic drug used for reduction of bleeding during major surgery. It is derived from lysine and works by inhibiting the transformation of plasmin to plasminogen and subsequently preventing the degradation of the formed clots [1]. Internal fixation of pelvic and acetabular fractures is considered one of the highest injuries associated with blood loss either during the injury itself or at the time of surgery and subsequently necessitates allogenic blood transfusion [2].

The average blood transfusion following fracture of the pelvis and acetabulum is 2 units in APC type I and reaches up to 12.6 units in APC III and 2.7–4 units in lateral compression fracture. In vertical shear fractures, the blood transfusion required reached up to 4.6 units in average. The group of fractures with highest need for blood transfusion was the APC III and LC III (up to 60% of patients). For acetabular fractures, the anterior column, anterior column with hemitransverse posterior, and the T type fracture required transfusion in 50% of cases. The largest reported number of blood units transfused was in transverse fracture (13 units), both column fracture (8.8 units) and anterior column with hemitransverse posterior (6.4 units) [3].

Patients with these types of pelvic and acetabular injuries are usually considered as polytrauma patients with mandatory

Level of evidence: level 3 evidence prospective randomized case control study.

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control and preservation of blood volume to avoid second hit phenomenon which might endanger patient homeostasis and initiate a secondary damage of tissues due to hypoxia [4].

Reducing blood loss in these cases represents an intraoperative challenge as it mandates appropriate control of bleeding with avoiding prolonged stoppage of anticoagulants for those nonambulant patients. Tranexamic acid (TXA) was introduced as a reasonable solution that can chemically reduce the amount of blood loss during surgery without inducing a hypercoagulable state which might end up with DVT or pulmonary embolization [1, 5, 6]. Several studies introduced the use of tranexamic acid as a local chemotherapeutic as in TKR or as a general usage as in major orthopaedic surgery [7, 8]. Reduction of bleeding during and after pelvic and acetabular surgery is considered also an important factor for early soft tissue healing and improvement of results besides decreasing the chances for haematoma collection and subsequent infection. However, a specified study to evaluate and prove TXA value during pelvic and acetabular fixation with limited complication in this type of bedridden patients is lacking.

The aim of this study is to evaluate the effectiveness of intravenous tranexamic acid injection before pelvic and acetabular surgery for reduction of blood loss and blood transfusion during and after surgery and to evaluate any possible complications for its use.

Material and methods

This prospective double blinded randomized case control study included 108 pelvic and acetabular surgeries in 97 patients admitted between the period of November 2017 until May 2021 with pelvic and acetabular fractures indicated for internal fixation. These cases were randomly divided between two groups; the first group (G1) received intravenous TXA ($N=54$) while the second group (G2) received a placebo only (control group, $N=54$) (Fig. 1). Randomization was carried out by the computer method and the study was approved by the research ethical committee in our institution and all included patients signed a separate informed consent on admission for inclusion in the study. Both surgeon and anaesthetist were blinded regarding patient groups.

The main inclusion criteria were pelvic or acetabular fracture indicated for open reduction internal fixation in an adult patient (≥ 18 years). Combined surgery including other major limb fixation simultaneously with the index procedure were excluded from this study. Patients with chest or abdominal injury with possible internal haemorrhage were also excluded from the study. Patients with minor injuries as upper extremity injuries with minimal expected bleeding were not excluded. Also, patients with medical treatment of any major blood disease that might affect coagulation or patient receiving anticoagulants for other diseases (e.g.,

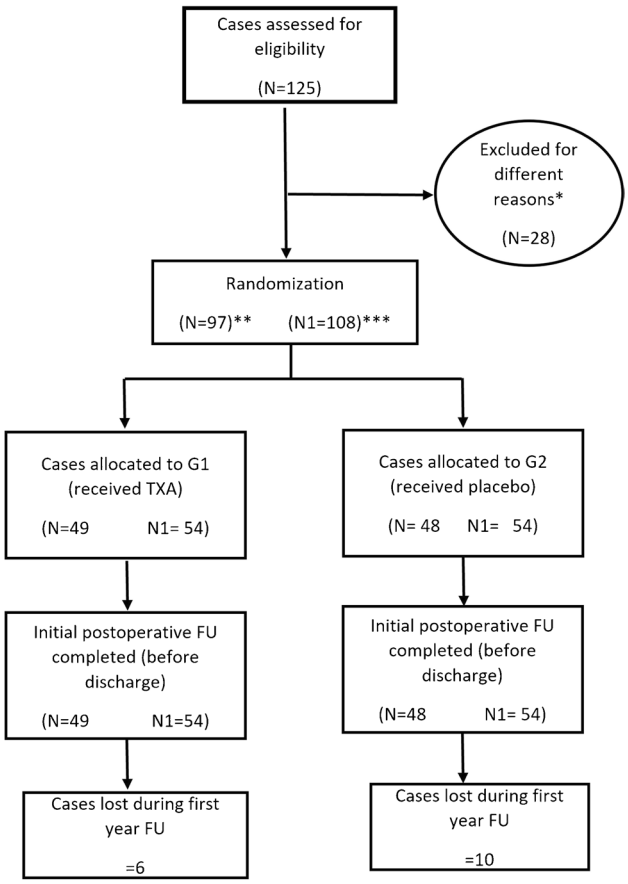

Fig. 1 Allocation flow chart for cases participated in this study. *Exclusion was due to either refusal of patients or presence of exclusion criteria. **N refers to number of patients. ***N1 refers to number of surgical procedures (some patients were approached with two separate procedures)

cardiovascular disease) were also excluded. Patients with injuries that might contraindicate the immediate use of anticoagulants were also excluded (traumatic intracranial haemorrhage). Patients with a known contraindication for the use of TXA were also excluded from this study. These contraindications included active traumatic brain injury, renal failure, smoking, OCP (oral contraceptive pills), pregnancy, known drug hypersensitivity, or former history of DVT (Table 1).

On admission, patients' general condition was evaluated including GCS, degree of shock, ABG, Hb, serum lactate, and coagulation profile according to the acute trauma life support and hospital trauma code activation protocol. Preoperative resuscitation was done and patients were prepared for surgery which was implemented by the same surgeon or under his supervision under general anaesthesia. All cases with APC type fracture pelvis were managed initially with a pelvic binder from which five cases were initially managed with an external fixator as damage control measure. Perioperative clinical evaluation of the patients included evaluation of pulse rate and blood pressuresix hourly before and on

the following first 48 hours after surgery. Laboratory evaluation included haemoglobin level (Hb), haematocrit (HCT) at the time of first TXA injection before surgery and immediately after surgery, 24 and 48 hours following surgery, and the amount of blood transfused to the patient perioperative (starting from time of TXA injection, during surgery, and on the first 48 hours following surgery). Fluid replacement intra-operative included crystalloid as well as blood products according to haemodynamic status and anesthesia management protocol. The drain was kept for the first 24–48 hours and the blood collected in the drain was estimated.

The trigger for preoperative transfusion is Hb level below 8 g/dL in a healthy patient and 9g/dL for cardiac patients as stated by S. Kashyap et al. [9]. Intra-operatively, due to lack of definite transfusion trigger, blood transfusion was judged by anaesthetist considering estimated blood loss, haemodynamics and tissue oxygenation, and intra-operative CBC evaluation. Post-operatively, the patient was indicated for blood transfusion to maintain Hb level above 8 g/dL or in the presence of symptoms such as chest pain, heart failure, orthostatic hypotension, or tachycardia unresponsive to fluid resuscitation according to the American Association of Blood Banks guidelines [10]. Post-operative VTE prophylaxis included low molecular weight heparin in the prophylactic dose started 8–12 hours after surgery and until adequate ambulation of the patient out of bed (around 30 days).

Patients were stratified into two groups; the first group (G1) received an average of 1 gm IV TXA (15 mg/kg per dose of TXA) after induction of anaesthesia, and 3 hs following the first dose and the second group (G2) received a placebo only (0.9 saline solution). The variables evaluated for comparison between groups included demographic data (age, gender), fracture-related variables (fracture classification, method of fixation and approach), and laboratory related variables (Hb, haematocrit value, total blood loss TBL, volume of blood transfused) and complications (DVT, infection) .

This study was based principally on evaluation of the total blood loss (TBL), level of Hb and haematocrit value pre/post-operative, and the evaluation of amount of blood transfused during surgery and in the first 48 hours post-operative as the primary outcome variables.

The total blood loss (TBL) was evaluated using the Nadler blood loss formula [11] for correlating the blood volume and Hb concentration and finally evaluating the amount lost relative to the initial Hb volume with consideration of the amount of blood transfused by haemoglobin balance method (Fig. 2) [11, 12]. The starting Hb level was estimated

Table 1 Patient demographics

		TXA (54)	Placebo (54)	Sig
Age	Mean ± sd	32.4 ± 10.9	37.9 ± 13.5	0.06
Gender	No. (%)			0.8
Male		39 (72.2)	37 (68.5)	
Female		15 (27.8)	17 (31.5)	
Type of fracture	No. (%)			0.8
Acetabulum		35 (64.8)	37 (68.5)	
Pelvis		19 (35.2)	17 (31.5)	
Fracture classification	No. (%)			0.3
Post wall ac		14 (25.9)	14 (25.9)	
Post column ac		7 (13.0)	5 (9.3)	
Ant column ac		5 (9.3)	4 (7.4)	
Transverse ac		4 (7.4)	5 (9.3)	
T type fracture ac		3 (5.6)	4 (7.4)	
Post wall and column ac		1 (1.9)	0	
Transverse and post wall ac		1 (1.9)	0	
Both column ac		1 (1.9)	5 (9.3)	
APC pelvis		15 (27.8)	9 (16.7)	
Lat compression pelvis		3 (5.6)	3 (5.6)	
VS type pelvis		1 (1.9)	5 (9.3)	
Mode of trauma	No. (%)			
Hemoglobin level on admission (g)	Mean ± sd	11.0 ± 1.2	10.3 ± 1.3	0.5
Hemoglobin level before surgery (at time of TXA injection) (g)	Mean ± sd	10.7 ± 1.5	10.1 ± 1.4	0.6
INR	Mean ± sd	1.3 ± 0.2	1.3 ± 0.2	0.5
Duration of follow-up (months)	Mean ± sd	25.7 ± 8.5	26.0 ± 7.4	0.8

Haemoglobin balance Method

$$\mathbf{BV} = k_1 \times H_3 + k_2 \times W + k_3$$

$$\mathbf{Hb}_{\mathbf{loss\ total}} = BV \times (Hbi - Hbe) \times 0.001 + Hbt$$

$$\mathbf{V}_{\mathbf{loss\ total}} = 1000 \times Hb_{loss\ total}/Hbi$$

1 U blood was calculated to contain
52 ± 5.4 g Hb

$Hb_{loss\ total}$ (g): The loss volume of Hb
Hbi (g/L): The Hb value before surgery
Hbe (g/L): The Hb value after surgery;
Hbt (g): The total volume of blood transfusion
BV (ml): The patient's blood volume before surgery
H (m): Height
W (kg): Weight
For males, $k_1 = 0.3669$, $k_2 = 0.03219$, and $k_3 = 0.6041$, while for females, $k_1 = 0.3561$, $k_2 = 0.03308$, and $k_3 = 0.1833$

Fig. 2 Method of calculation of blood volume and TBL

from the blood sample taken at the time of infusion of TXA during surgery. The single transfusion blood unit was considered to add 55 g to the Hb level [13]. The final Hb level was considered from the sample taken 48 hours after surgery (cut-off point of the study).

Sample size was calculated using a pre hoc test depending on the number of patients in a former study carried out by Spitler et al. on TXA on a similar study sample [13]. The effect size calculation relied on the amount of blood units expected to be transfused to the patients. The study variables were tested for normality using one sample K-S test. Significant differences between both groups were tested using chi-square test for categorical variables and *t*-test for normal continuous variables and Wilcoxon test for non-normal variables. The correlation was tested using Pearson correlation test as appropriate. $p \leq 0.05$ was considered significant (Fig. 3).

Results

There was no significant difference between both groups with regard to age, mechanism of injury, or fracture classification with normal distribution of variables (Table 1 and 2). The calculated TBL was 829.7 ± 219.2 ml in G1 and 1036.9 ± 314.9 ml in G2 while the blood units transfused were 51.9 ± 40.5 g in G1 and in 83.5 ± 85.3 g G2 (Table 3). The other variables' results (Hb, haematocrit value, operative time, IBL) are shown in Table 2 and 3. There was a significant difference between both groups regarding the TBL and the blood units given with less blood loss and less blood units transfused in G1 .

The total blood units transfused were statistically significant in the TXA group (Table 3). The average blood units transfused in G1 was 52.4 ± 40 g, while it was larger in G2; 89.4 ± 60.6 g ($p = 0.002$) (Table 4 and 5).

The complications recorded were DVT in 3 patients in G1 and 1 patient in G2. Superficial infection in 1 patient in G1. Pulmonary embolism was diagnosed in five cases: three in G1 and two in G2, however with complete improvement. No deep infection was recorded in both groups. Two patients showed heterotopic ossification in G2 with prolonged follow-up of cases and one patient with sciatic nerve injury in each group (Figure 4 and 5).

Discussion

The study showed clear evidence that TXA injection can decrease the peri-operative blood loss and the need for blood transfusion in pelvic and acetabular surgery. TXA was used to decrease blood loss during various operations as with TKA and THA [5, 7, 8]. However, fractures

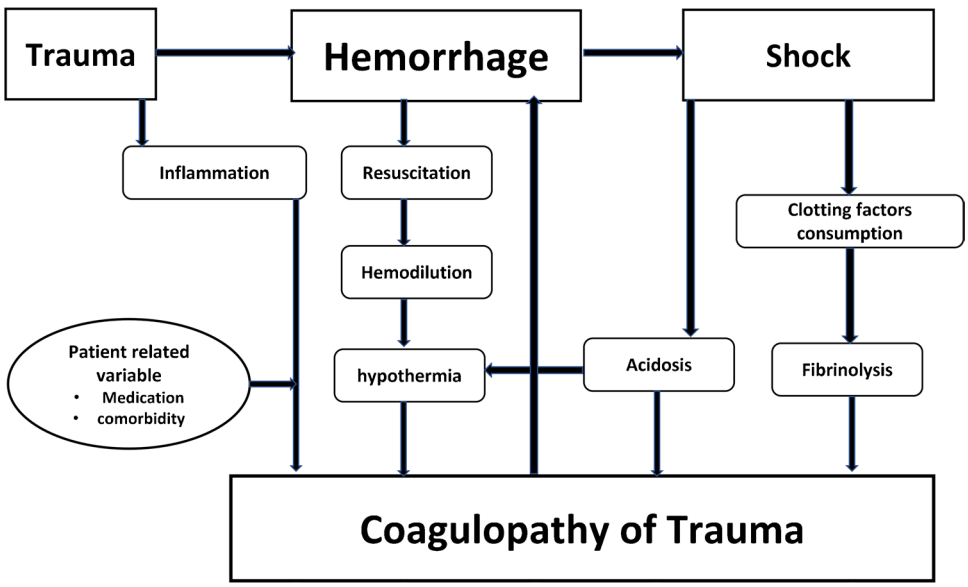

Fig. 3 Pathways contributing to coagulopathy in polytrauma patients

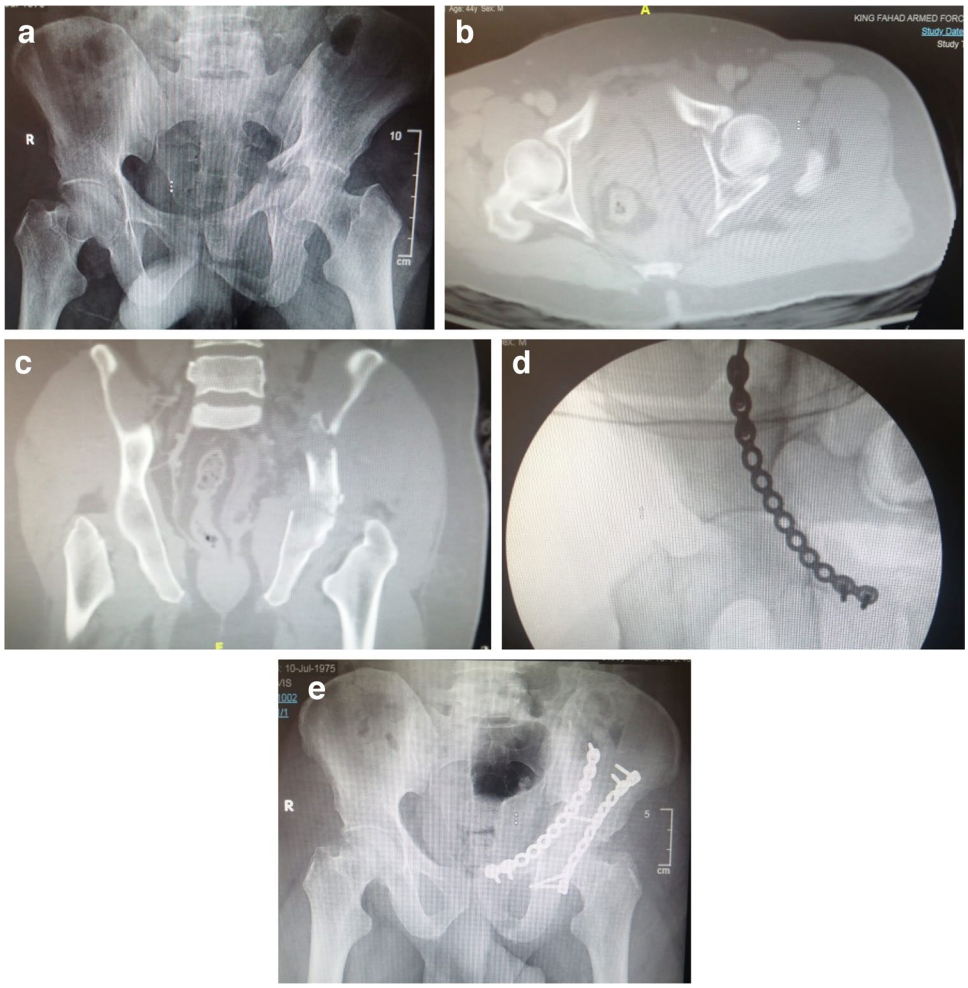

Fig. 4 a–e Fracture acetabulum T-shaped fracture: first surgery: (G1-TXA), anterior approach; Stoppa, second surgery: (G2-placebo), posterior approach; K-L approach

Table 2 Surgery-related data

		TXA (54)	Placebo (54)	Sig
Duration until surgery	Mean ± sd	3.2 ± 1.8	3.8 ± 2.6	0.2
Type of surgery	No. (%)			0.4
Anterior acetabulum app.		7 (13.0)	7 (13.0)	
Posterior or posterolateral .acetabulum app.		22 (40.7)	22 (40.7)	
Combined approach acetabulum		5 (9.3)	8 (14.8)	
Anterior . pelvis app.		4 (7.4)	2 (3.7)	
Posterior fixation of pelvic ring anterior to SI joint		3 (5.6)	4 (7.4)	
Anterior plating and posterior SI jiont screws		10 (18.5)	4 (7.4)	
Anterior plating and anterior SI jiont plating		3 (5.6)	4 (7.4)	
Anterior plating and posterior SI jiont fixation		0	3 (5.6)	
Operative time (minutes)	Mean ± sd	267.9 ± 61.3	297.9 ± 71.2	0.2
Intra-operative blood loss IBL (ml)	Mean ± sd	747.5 ± 207.6	917.7 ± 277.1	≤ 0.000

of the pelvis and acetabulum which are also considered surgical procedures with high expected blood loss were less evaluated with regard to the effect of TXA on bleeding with these patients. The TBL was estimated in cases with fracture pelvis to be around 476 ± 535 in type C1 compared to 1005 ± 649 mL in type C3 pelvic injuries [14]. Blackmore evaluated the needed blood transfusion in a large series of pelvic fractures and found that almost 55% of his patients received one or more blood units and almost 34% received six or more units in the first 72 hours following fracture

Table 3 Distribution of means of blood transfused, total hemoglobin loss, total volume loss (TBL) and final hematocrit value between TXA and placebo groups

	TXA	Placebo	Sig
	Mean ± sd	Mean ± sd	*p*
Blood transfused (g)	51.9 ± 40.5	83.5 ± 85.3	0.004 (Wilcoxon test)
Total hemoglobin loss (mL)	88.6 ± 23.7	102.8 ± 29.4	0.04
Total volume loss TBL (mL)	829.7 ± 219.2	1036.9 ± 314.9	0.001

[2]. The mean blood transfusion volume was recorded as 437.76 ± 282.02 mL for type A, 1603.13 ± 1203.28 mL for type B, and 2191.30 ± 1740.93 mL for type C pelvic fractures. Transfusion was greatest in APC III (12.6 units) and vertical shear (4.6 units) injuries [4]. On the other hand, both column (8.8 units) and anterior column posterior hemi-transverse (6.4 units) received the largest transfusions as reported by Magnussen et al. [3].

TXA is an ideal drug expected to reduce blood loss and consequently the need for blood transfusion in these complex cases with high demand for intra-operative and post-operative transfusion [5]. However, patients with pelvic and acetabular fractures are expected to have prolonged bed stay for variable periods according to type of fracture and management which is different than joint replacement cases which usually start ambulation on the first day post-operative [15, 16]. This prolonged bed stay in fracture patients particularly in pelvic and acetabular cases might add to the possibility and risk of DVT particularly with repeated blood transfusion and with the addition of a drug like TXA. Hence, the safe use of this drug is mandatory to be proved before its use to avoid such complications.

This study evaluated primarily the efficacy of the use of TXA in pelvic and acetabular surgery through estimating the amount of blood loss and blood transfused for each patient in the study starting from the point of administration of the drug and for the next 48 hours after surgery. The estimation of blood loss during that period utilized the haemoglobin dilution formula. Several formulas were interpreted by several authors for calculation of blood loss including haemoglobin balance and Ostheo formula as well as the haemoglobin dilution method with variable efficiency [12].

Another method was included in our study to overcome the described low accuracy of these formulas in calculating blood loss which is the gravimetric method for calculating blood loss intra-operatively (IBL) [17] and calculating the post-operative blood in the drain.

The allogenic blood transfusion especially through the liberal protocol is not preferable nowadays to avoid the associating complications specially the risk of disease transmission particularly HIV and hepatitis C, as well as the risk of acute life-threatening immune response [18, 19]. However,

Table 5 Correlation between operative time and starting hemoglobin with final outcome measures

	Operative time		Starting hemoglobin at time of injection of TXA	
	(*r*)	Sig. (*p*)	(*r*)	Sig. (*p*)
Blood transfused (g)	0.5	≤0.000	−0.8	≤0.000
Total hemoglobin loss (mL)	0.2	0.03	0.2	0.03
Total volume loss (mL)	0.4	≤0.000	−0.3	0.001

Table 4 Correlation between type of surgery and final outcome

Type of surgery	Blood transfused (g)	Sig		Total hemoglobin loss (mL)	Sig		Total volume loss (mL)	Sig	
		f	*p*		*f*	*p*		*f*	*p*
Anterior acetabulum app.	51.1 ± 33.9	7.5	≤0.000	95.6 ± 12.0	2.6	0.008	895.5 ± 123.4	3.1	0.002
Posterior or posterolat acetabulum app.	42.5 ± 45.7			102.8 ± 31.0			910.5 ± 287.5		
Combined approach acetabulum	118.5 ± 44.0			104.0 ± 33.0			1164 ± 404.7		
Anterior pelvis app.	36.7 ± 28.4			77.0 ± 23.3			682.5 ± 150.4		
Posterior fixation of pelvic ring anterior to SI joint	102.1 ± 49.5			87.0 ± 20.4			946.3 ± 288.7		
Anterior plating and posteriorant SIjoint screws	78.6 ± 35.5			74.8 ± 16.5			816.3 ± 186		
Anterior plating and anterior SI joint plating	125.7 ± 61.2			108.7 ± 19.2			1181.5 ± 267.1		
Anterior plating and posterior SI joint fixation	91.7 ± 31.8			80.1 ± 5.9			881.3 ± 73.1		

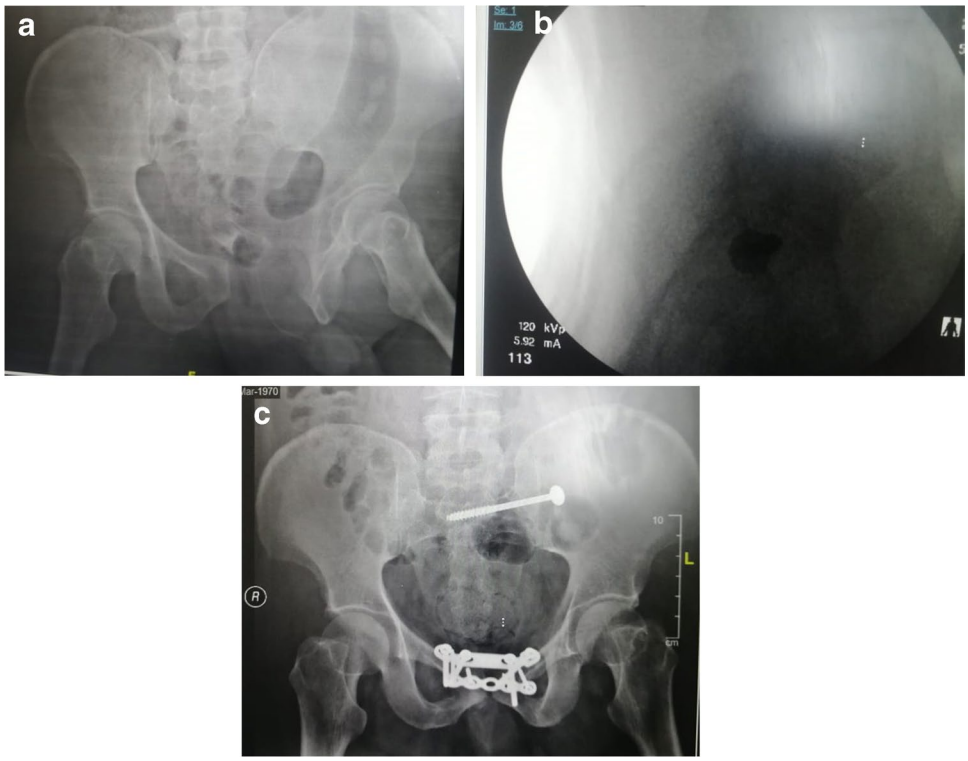

Fig. 5 a–c Fracture pelvis APC, (G2-placebo), anterior ring fixation + closed SI joint screw fixation

blood transfusion and maintenance of blood volume and Hb were confirmed to improve outcome in trauma patients with improvement of quality of life and possibly decreasing mortality and infection [4, 20].

Several studies were able to prove the efficacy and safety of TXA in joint replacement and spine surgeries in control of bleeding and reducing the need for transfusion [7, 8, 21, 22]. However, in trauma patients, the main focus of routine use of TXA was directed to hip surgery with limited description of its value on pelvic and acetabular fractures [23–25]. Moreover, two large series failed to prove the efficacy of TXA in these major injuries [13, 26]. Spitler et al. combined the evaluation of TXA effect on both hip patients as well and pelvic and acetabular patients and proved reduction of blood loss but with no significance with regard to the need for blood transfusion [13]. Piggott et al. were not able to find a clear relationship between the use of TXA in pelvic and acetabular fractures and reduction of blood loss as a routine use [27]. Seyit et al. found that using TXA in pelvic and acetabular surgeries was effective in decreasing blood loss and Hb drop and transfusion rates with no increase of complications particularly thromboembolic complications [28]. Adams et al. found that the results of TXA injection are encouraging in hip fractures that it significantly lowers the overall blood loss and the need for blood transfusion. On the other hand, in pelvic and acetabular surgery, the results are not supporting the same findings [29]. Both Lack and Spitler et al. concluded no effect of TXA on reduction of the amount of blood transfusion in pelvic and acetabular fractures [13, 26]. However, Spitlers et al. found significant reduction of the amount of blood loss with TXA use which was not congruent with the number of blood units transfused [13]. This study proved significant reduction in blood loss when estimated by the haemoglobin balance formula (Fig. 2). The intra-operative blood loss (IBL) calculated by the gravimetric method and blood units transfused were also reduced significantly in the group using TXA.

Regarding the safety of TXA, it was proved in arthroplasty and spine surgery patients not to increase the risk for VTE. However, with polytrauma patients, particularly with severe injuries like pelvic and acetabular fractures, the activation of complement system as a part of the physiological response to trauma might have its impact on patients with the use of TXA (Figure 3). In our study, there was no increase in the risk of VTE in patients using TXA. This might support the conclusion of Benoni et al. who described the efficacy of TXA only outside the vascular compartment [30]. For this reason, strict evaluation of patients' coagulation profile was done during the period of treatment with strict anticoagulant application. Regarding DVT and pulmonary embolism, the study did not support any significant difference between both groups with apparently a smaller number of DVT cases in the placebo group. This insignificant increase of cases in the TXA group can be attributed to patient-related variables such as patient age, obesity, and multiple traumas which

were noticed from the Caprini DVT risk screening [31] with higher level in these patients.

The main drawback in this study is the variability of the type of fracture, approach and starting haemoglobin at time of injection of TXA which will definitely affect the duration of surgery and blood loss (Table 4 and 5). Several questions were provoked regarding the accuracy of the formulas used for calculation of blood loss during and after surgery. Accordingly, we used the haemoglobin balance method for TBL and the gravimetric method for IBL in a trial to increase the chance of accuracy of this calculation. The variable haemodynamic situations of these polytrauma patients and their generalized body response to trauma are other variables which might inadvertently have a considerable effect on this type of studies particularly with activation of variable body responses including the complement system.

In conclusion, TXA can be used safely to reduce the blood loss and the need for blood transfusion in the event of pelvic and acetabular fractures.

Acknowledgements We would like to thank Dr. Abdel-Hady D., Department of Community Medicine, Mansoura University, for performing the design of the study and the statistics.

Author contribution *Mohamed MF Sharaby*: formulate research hypothesis, construction of proposal, submitting research approval, calculation of sample size, statistical analysis, data collection, literature review and drafting manuscript, submission of paper; *Younes M El-Deeb*: refining research idea, data collection, literature review, review manuscript.

Data availability Patient data are available on request.

Declarations

Ethical committee approval This study was approved by the research ethical committee in armed forces hospital southern region code no: AFHSRMREC/2017/orthopedics/508. All patients were consented to participate in the study and to publish the data including patients in the placebo group. Informed verbal consent for participation and publication of the paper was insured from all patients after explaining the aim and objectives of the study. Patient participation was voluntary and patient confidentiality was insured.

Conflict of interest The authors declare no competing interests.

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