Archives of Orthopaedic and Trauma Surgery
https://doi.org/10.1007/s00402-024-05325-2

TRAUMA SURGERY

A randomised controlled trial assessing the effect of tranexamic acid on post-operative blood transfusions in patient with intra-capsular hip fractures treated with hemi- or total hip arthroplasty

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Received: 31 January 2024 / Accepted: 12 April 2024

Abstract

Background Intravenous tranexamic acid (TA) has proven efficacy in reducing blood loss and incidence of transfusion of blood products in elective total joint arthroplasty. However, evidence of efficacy in the setting of intracapsular hip fractures needing hip hemiarthroplasty (HA) or total hip arthroplasty (THA) are scarce. This study aimed to assess post-operative transfusion incidence in this clinical setting.

Methods Over a five-year period 250 patients with intracapsular neck of femur fractures requiring arthroplasty were randomised to two groups. The treatment group received three-dose intravenous TA protocol and the control group received usual treatment without administration of TA. Blood loss was estimated from the change in Hb levels on day 1, 3 and 5 after surgery compared to preoperative levels. Transfusions of blood products were recorded when they were triggered by an a priori protocol. Post-operative complications were recorded during patient hospital admission.

Results The intervention group showed significantly lower transfusion incidence of packed red blood cells (PRBC) (6 vs. 15, $p=0.04$, OR = 0.37, 95%CI OR = 0.14 to 0.99) and in the group of patients who received a blood transfusion, a trend was observed for patients who received TA to have lesser number of units of PRBC (mean = 1.3 vs. 1.6, $p=0.51$). A significant difference was noted in post-operative Hb levels of day 1,3 and 5. Backward stepwise multivariable regression analysis showed the use of TA was the most significant factor for reduction in postoperative blood transfusion ($p=0.047$, OR = 0.37, 95% CI OR = 0.14 to 0.99). Assessment of the strength of the correlation showed modest correlation (Pearson correlation −0.13 $p=0.04$, 95% CI correlation= -0.25 to -0.01). There was no increase in adverse events in patients who received TA.

Conclusion The use of TA in setting of intracapsular hip fractures requiring arthroplasty reduces blood loss, the need for transfusion of blood products and may reduce surgical site complications without increasing the risk of VTE.

Keywords Hip arthroplasty · Tranexamic acid · Venous thromboembolism · Neck of femur fracture · Blood transfusion

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Published online: 07 June 2024

Introduction

Displaced intracapsular neck of femur fractures (NOF) are a common condition usually managed surgically with either hemiarthroplasty (HA) of the hip or total hip arthroplasty (THA). As the elderly population grows, the number of hip fractures continues to increase. The Australian population is classified as a moderate risk for hip fracture with an incidence of new hip fractures of 250/100,000 men and women [1]. The Australian Orthopaedic Association National Joint Registry reported on 24,801 primary THA procedures and 89,257 HA procedures with a diagnosis of fractured neck of femur [2].

There is a recognized drop in haemoglobin (Hb) level after fracture NOF due to blood loss which varies depending on fracture type, location and the type of surgical procedure used. Intracapsular NOF fractures are estimated to lead to a preoperative drop in Hb of 14.9 g/L [3] especially if there is delay in surgery. Perioperative treatment of these fractures is associated with a significant rate of allogenic blood transfusion with a transfusion index of 1.8–2.08 units of packed red blood cells (PRBC) per transfused patient [4, 5]. The transfusion rate in NOF fracture patients is reported between 29 and 53% [4–8]. The transfusion rate varies according to type of procedure performed with hemiarthroplasty patients requiring blood transfusion in 26–52% of cases [6, 7, 9, 10], and 40–45% of THA cases [6, 7]. Transfusion of blood products is a recognized factor in clinical and functional outcomes post-surgery with associated morbidity, financial cost and increased hospital length of stay [11–14].

There is ample evidence for the safety and efficacy of Tranexamic acid (TA) in reducing post-operative blood loss after THA in the elective setting [15–18]. Meta-analyses of published randomised controlled trials show efficacy of intravenous TA for reducing blood loss and transfusion in hip surgery patients who had their fracture internally fixed [19–21]. There is, however; scant high-level evidence about the utility of TA in hip fracture surgery needing arthroplasty [22–27] despite evidence to show that arthroplasty surgery is associated with a higher degree of blood loss compared to surgery for fracture fixation [3, 28, 29].

A Cochrane Collaboration systematic review [30] showed that TA reduced the need for blood transfusion by 30% in the emergency surgery setting without increase in pulmonary embolism (PE) or myocardial infarction (MI), but uncertain effects on the rate of deep venous thrombosis (DVT) and stroke. The incidences of these complications in the setting of NOF fractures in published literature is 1.6% DVT, 0.5% non-fatal PE and 0.5% fatal PE [19].

The hypothesis for this study was administration of intravenous TA in patients presenting with intra-capsular neck of femur fractures undergoing hemiarthroplasty or total hip arthroplasty reduces the rate of allogenic blood transfusion within the first post-operative week.

The primary aim of this study was to assess if blood transfusions were reduced by the use of TA. Secondary aims were to assess if TA reduced haemoglobin drop at 1, 3 and 5 days after surgery; and to assess if the use of TA was associated with increased incidence of post-operative VTE, cardiovascular or cerebrovascular events in this population.

Materials and methods

This randomised controlled trial was conducted after approval from the institution's Health Research and Ethics Committee (HREC/14/Nepean 114, local reference 14/57) and the trial protocol was registered with Australia and New Zealand Clinical Trials Registry (ANZCTR) http://www.ANZCTR.org.au/ACTRN12617000391370.aspx (registration number ACTRN12617000391370, UTN: U1111-1189-6122, registered 16/03/2017). All patients who were admitted to our department with intra-capsular neck of femur fractures requiring treatment with hemiarthroplasty (cemented or uncemented) or total hip arthroplasty (cemented, hybrid or uncemented) within 48 h from the time of injury were approached for recruitment into the study. After obtaining consent from patients; or from their guardian, spouse, de facto partner or closest living blood relative in cases of impaired capacity for consent, we used four letter block randomisation to allocate patients to one of two treatment groups: a group which received TA (Group A) according to a designated intravenous three-dose protocol, and a second group (Group B) were managed with the usual standard of care from the orthopaedic and geriatric team without administration of perioperative TA.

Tranexamic acid was administered in the form of intravenous medication (Tranexamic Link 500 mg/5mL ampoules, $2.64AUD per ampoule) at the time of skin incision and at 8 and 16 h after surgery. Patients were administered 15 mg/kg for each dose. In accordance with the product information, the dose of TA was reduced in patients with impaired renal function. If patient estimated glomerular filtration rate (eGFR) was between 60 and 89 ml/min, the second and third dose was 11.25 mg/kg. If the eGFR was 30–59 ml/min, the second and third dose were 6.3 mg/kg.

Patients were excluded if informed consent was not obtained, if they had delay to surgery of more than 48 h from the time of injury, if the neck of femur fracture was extra-capsular or if it was treated by internal fixation e.g. by cannulated screws, dynamic hip screw or intra-medullary nail device. Patients were also excluded if they had a contraindication to the use of TA as per the product consumer information (Appendix A).

Patients were allowed treatment with various anaesthetic modalities based on their needs. We recorded the different modalities of anaesthetic used including the use of spinal and regional anaesthesia which may influence perioperative blood loss [31–33]. Study investigators and participants were not blinded to treatment group. Each patient had a study dedicated medication chart concealed in an envelope. This medication chart had 'TA' charted for the treatment group and 'No TA' in the control group patients. Patients were assessed for the need of blood transfusion during the first week of admission. The trigger for blood transfusions was according to 'NHMRC Clinical Practice Guidelines on the Use of Blood Transfusion' (Appendix B). Patients with Haemoglobin level between 70 and 100 were transfused if they had persistent tachycardia > 100 bpm or systolic blood pressure < 100mmHg. The decision to prescribe a blood transfusion was made by the orthogeriatric team who were blinded to the treatment arm. The reason for blood transfusion and the number of units transfused and the compliance with these guidelines were recorded.

To estimate blood loss the change in haemoglobin (Hb) was recorded by measuring the pre-operative levels and Hb levels on day 1, 3 and 5 after surgery. The occurrence of thromboembolic events, AMI or CVA were recorded. Non-blinding in this study was not expected to interfere with measurement of this objective data.

For thromboembolic prophylaxis, on admission all patients were commenced on mechanical (calf compressors and/or graduated compression stockings-TEDS) and chemical venous thromboembolic prophylaxis with subcutaneous Low Molecular Weight Heparin (LMWH)- Enoxaparin. Patients received a standard Enoxaparin dose of 40 mg/day. If eGFR was less than 30mL/min, or total body weight less than 50 kg, patients received 20 mg/day only.

Statistical analysis

Intention to treat analysis was performed in the primary analysis. Per protocol analysis was conducted to account for any cross over between the groups during the conduct of the study. The primary study outcome was to determine the effect of administration of a three-dose protocol of intravenous TA on the incidence of acute postoperative blood transfusion in patients presenting with intra capsular neck of femur fractures undergoing hemiarthroplasty or total hip arthroplasty. The secondary outcomes were to assess the change in postoperative Hb levels on day 1,3 and 5 after surgery to estimate blood loss; and to assess the safety of use of TA by assessing the incidence of acute post-operative complications during hospital admission, specifically venous thromboembolic events (deep vein thrombosis, pulmonary embolism), cardiovascular events (acute myocardial infarction) and cerebrovascular events (stroke) in this study population.

The student's t-test was used to analyse continuous variables. Pearson chi square test was used to compare categorical variables. The strength of any significant association was tested in multivariable regression analysis using backward step-wise analysis model. The strength of any correlation was tested using the Pearson correlation test. Missing data were not imputed. Analyses were carried out using International Business Machines Statistical Package for the Social Sciences (IBM SPSS) software, version 28.0 (IBM, Armonk, NY, USA). All reported p-values were two-sided, and $p < 0.05$ was considered statistically significant.

A priori power calculation was performed based on an 80% power to detect a clinically important difference of 20% reduction in blood transfusion at a significance level of 0.05, 103 patients were required in each group. Allowing for 20% loss to follow up, we recruited 125 patients in each group.

Results

Between 05/01/2017 and 23/12/2021 there were 409 admissions to our unit for patients with intra-capsular neck of femur fractures requiring either total hip arthroplasty or hemiarthroplasty. Palliative management was commenced in the emergency department for four patients; and two patients requested transfer to other institutions for their treatment. All eligible patients were assessed for inclusion in study and 318 were eligible to participate. After 68 patients declined to participate, 250 patients were randomised to receive TA (Group A) or not to receive TA (Group B) (Fig. 1). Demographic data of patients who participated in this study were recorded in Table 1. There were no significant differences between the two study groups for any of the demographic, anaesthetic factors or type of operation performed. In Group A, three patients did not receive TA and two patients received one dose only prior to incision. In Group B, five patients received single dose TA prior to incision and three patients received three doses of TA. The compliance with the study protocol was high, 96% in both groups.

Based on an intention to treat analysis, we found in Group A participants, who were randomised to receive TA, there were significantly fewer patients who received transfusion of packed red blood cells (PRBC) units (Table 2). When patients received a transfusion, there was only a weak trend for patients who received TA to have lesser number of units of PRBC (mean = 1.3 units, SD = 0.52, range = 1 to 2 units) compared to the group of patients who did not receive TA (mean = 1.6 units, SD = 0.91, range = 1 to 4 units) $p = 0.51$, mean difference = 0.27, 95% CI of difference −0.57 to

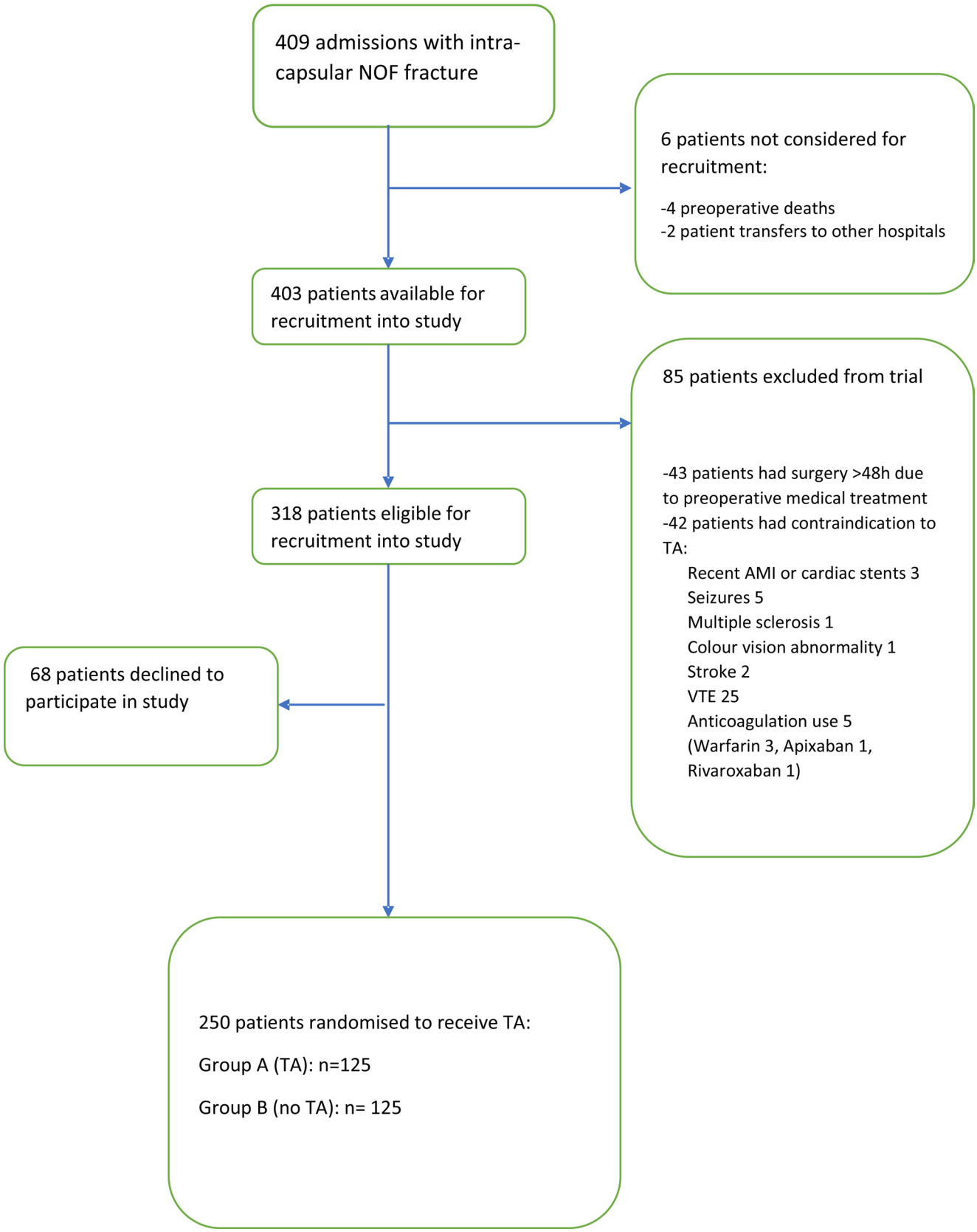

Fig. 1 Flow diagram of patient recruitment into the study and reasons for exclusion

Table 1 Baseline data of patients recruited to the study. A total of 250 patients were randomised to receive Tranexamic acid (TA) (Group A) or not to receive TA (Group B). ASA: American Society of Anesthesiologists Classification, Hb: Haemoglobin, THA: Total hip arthroplasty

	Group A (TA given, $n=125$)			Group B (No TA, $n=125$)			
	n (%)	Mean (SD)	Range	n (%)	Mean (SD)	Range	*p*-value
Age		79 (10.8)	45–97		82 (9.5)	51–102	0.08
Female	86 (68.8)			86 (69.0)			1.00
Charlson index		5.20 (1.8)	0–10		5.30 (1.6)	1–10	0.62
ASA							
1	2 (1.6)			1 (0.8)			0.98
2	32 (25.6)			31 (24.8)			
3	71 (56.8)			72 (57.6)			
4	19 (15.2)			20 (16.0)			
5	1 (0.8)			1 (0.8)			
Type of anaesthesia							
General anaesthesia	113 (90.4)			107 (85.6)			0.24
Spinal anaesthesia	12 (9.6)			18 (14.4)			
Regional anaesthetic block	43 (34.4)			58 (46.4)			0.05
Baseline Hb (g/L)		128 (15.3)	87–163		128 (16.1)	82–176	0.75
Hemiarthroplasty	94 (75.2)			98 (78.4)			0.65
THA	31 (24.8)			27 (21.6)			

Table 2 Analysis of blood transfusion trends and haemoglobin (Hb) changes between the study groups. 'Change Hb' refers to the change in the measured haemoglobin values in the post-operative period (day 1,3 and 5 after surgery) compared to the pre-operative haemoglobin value. PRBC: Packed red blood cells, Hb: Haemoglobin levels (g/L)

	Group A (TA given, $n=125$)	Group B (No TA, $n=125$)	p-value	Odds ratio or Mean difference	95% CI OR
Number of patients required blood transfusion, *n (%)*	6 (4.8)	15 (12.0)	0.04	0.37	0.14 to 0.99
Blood transfusion (Units PRBC), *mean (range)*	1.3 (1–2)	1.6 (1–4)	0.51	0.27	-0.57 to 1.10
Baseline Hb (g/L) mean (SD)	128 (15.3)	128 (16.1)	0.75	-0.64	-4.56 to 3.28
Day 1 Hb (g/L) mean (SD)	111 (15.6)	106 (15.9)	0.013	-5.04	-8.98 to -1.09
Day 3 Hb (g/L) mean (SD)	108 (15.6)	101 (15.5)	0.003	-6.12	-10.14 to -2.09
Day 5 Hb (g/L) mean (SD)	106 (16.1)	100 (14.0)	0.008	-5.68	-9.89 to -1.47
Change Hb Day1 mean (SD)	-18 (11.9)	-22 (12.1)	0.003	-4.74	-7.85 to -1.63
Change Hb Day3 mean (SD)	-21 (12.4)	-26 (13.2)	0.002	-5.61	-9.04 to -2.17
Change Hb Day5 mean (SD)	-22 (14.2)	-27 (13.1)	0.007	-5.45	-9.39 to -1.51

Table 3 Analysis of the complication rates between the two study groups. SSI: surgical site infection, CVS: cardiovascular complications including ischaemic heart disease, acute myocardial ischaemia, arrhythmia. VTE: venous thromboembolic events including deep venous thrombosis (DVT) and pulmonary embolus (PE). Other complications refer to the development of other adverse events such as urinary tract infections, acute renal injuries, pneumonia, gastrointestinal bleeding, bowel obstruction

	Group A (TA given, $n=125$)	Group B (No TA, $n=125$)	p-value	OR	95% CI OR
SSI	0 (0)	3 (2.4%)	0.25	0.49	0.44–0.56
CVS	3 (2.4%)	3 (2.4%)	1.00	1.00	0.20–5.05
VTE	4 (3.2%)	3 (2.4%)	1.00	1.34	0.30–6.13
Death	2 (1.6%)	3 (2.4%)	1.00	0.66	0.11–4.03
Other Complications	17 (13.6%)	21 (16.8%)	0.48	0.78	0.39–1.56

1.10). This is likely because most patients were not transfused unless the Hb levels were below 80 g/L, thus requiring at least 2 units PRBS to bring Hb levels above 100 g/L.

There were no significant differences in patient Hb levels on presentation, but a significant difference was noted in post-operative Hb levels of day 1,3 and 5 between the two groups with significantly less drops in Hb compared to baseline levels in the TA group (Table 2).

There was no increase in adverse events in patients who received TA (Table 3). A trend was observed for lower overall complications; particularly, lower wound healing complications possibly related to less swelling and haematoma around the surgical site. The overall incidence of inpatient VTE was 2.8%. Three patients in each group ($n=125$) developed a post-operative DVT. There was single case of PE in a patient who received three doses of TA. An audit of records showed that all patients received mechanical and chemical DVT prophylaxis as per protocol.

Per protocol analysis was conducted to account for 10 patients in whom there was cross over between the randomisation groups. This showed statistically significant difference in patient age and the number of THA performed, but no significant differences in the number of patients who required a blood transfusion; or in the number of patients who experienced a complication (Appendix C).

Backward stepwise multivariable regression analysis of factors associated with receiving a blood transfusion in patients undergoing hemiarthroplasty or total hip arthroplasty after intracapsular neck of femur fracture was performed. This took into account the following clinically important variables: age, gender, ASA classification, Charlson index, operation type and the use of Tranexamic acid. This regression analysis showed the most significant factor for reduction in postoperative blood transfusion is the use of tranexamic acid ($p = 0.047$, OR = 0.37, 95% CI OR = 0.14 to 0.99). Assessment of the strength of the correlation showed modest correlation (Pearson correlation -0.13 $p = 0.04$, 95% CI correlation= -0.25 to -0.01).

Discussion

Neck of femur (NOF) fracture patients are amongst the frailest patients treated by orthopaedic surgeons with one year mortality between 14 and 36% [34, 35]. A key surgical principle is to limit blood loss and minimise the need for post operative transfusion in these patients. Blood transfusion, regardless of the amount of transfusion, is associated with increased hospital length of stay [13], periprosthetic infection [36–38] and long-term mortality after hip fracture surgery [39]. The main finding of this study was significantly fewer patients with NOF fracture operated on within 48 h of presentation required blood transfusion after hip hemiarthroplasty or total hip arthroplasty. This study also found there was significantly less reduction in haemoglobin levels after surgery in patients who received a three-dose TA protocol.

TA is widely used to reduce blood losses and transfusion requirements following elective hip or knee arthroplasty and it has been shown to confer these benefits irrespective of the route of administration [40–42]. This study used an intravenous, three-dose TA protocol shown to be the most effective protocol for the reduction in blood loss and postoperative blood transfusion [43].

A secondary finding was no increase in adverse events in patients who received TA. There were no cases of mortality in either group, but this is largely limited by short patient follow up being limited to the acute admission to the orthopaedic unit. A trend was observed for lower overall complications; particularly, lower wound healing complications, possibly related to less swelling and haematoma around the surgical site. The overall incidence of VTE during admission was 2.8% which was low; and consistent with findings of previous studies in a similar setting [20, 44–46].

The use of TA during hip arthroplasty in fracture setting is studied less frequently compared to elective hip arthroplasty due to fears of increased complications in this patient population with complex comorbidities treated with various medications including anticoagulants. While a number of studies showed a reduction in blood transfusion in patients who received TA during hip hemiarthroplasty or total hip arthroplasty [22–27, 44, 45, 47, 48], many were limited by their retrospective design [22–25, 45], small patient numbers [48], limiting the study population to relatively healthy patients [47] or by including all types of NOF fractures including those requiring screw, plate or nail fixation where the risk of transfusion is lower than arthroplasty [26].

In this study, an a priori power calculation was conducted to detect a clinically important difference of 20% reduction in blood transfusion. The study results showed a significant reduction (40%, $p = 0.04$) in the number of patients who required a transfusion of at least one unit of packed RBC. The transfusion protocol meant that most patients received 1–2 units of packed RBC when a transfusion was needed; therefore, this study did not detect a significant difference in the number of packed RBC units in patients who received a transfusion.

This study has a number of limitations, chief amongst them is the limited patient follow up to the immediate surgical admission. This was due to limited capacity to follow up this elderly population in the outpatient setting as many were discharged to nursing homes and other care facilities. The occurrence of a clinically symptomatic VTE was recorded, but we were unable to routinely screen every patient for the occurrence of DVT with a routine doppler ultrasound.

In this study, blinding of investigators to the use of TA was not permitted by the institution's ethics board, but we attempted to conceal the use of TA by recording it on a separate medication chart stored separate to the patient notes and kept concealed from the orthogeriatric team who made the decision for a blood transfusion when required according to the prescribed guidelines. Therefore, we believe the decision for transfusion in this study was not significantly affected by the lack of blinding.

Haemoglobin values are an objective way of measuring post-operative blood loss, but they should be interpreted with caution as they can be falsely elevated due to dehydration or under resuscitation, especially in this elderly population.

Conclusion

This study showed that three-dose intravenous TA administration significantly reduced the number of patients who received allogenic blood transfusion in the setting of intracapsular NOF fracture treated with hip hemi- or total-arthroplasty within 48 h of presentation. There was less drop in post-operative haemoglobin levels and a trend for less post-operative complications with no increase in VTE.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00402-024-05325-2.

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