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ORIGINAL STUDY

Low blood transfusion rate after implementation of tranexamic acid for fast-track hip- and knee arthroplasty. An observational study of 5205 patients

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The purpose of this study was to retrospectively evaluate the efficacy of a tranexamic acid (TXA) perioperative protocol for primary hip- and knee arthroplasty, in terms of allogenic blood transfusion rates. A retrospective cohort study was conducted and included all primary hip and knee arthroplasty procedures in the period of 2014-2019. Patients who underwent surgery due to trauma or revision were excluded. A total amount of 5205 patients were eligible for inclusion. Two equal and weight depending doses of TXA were given, preoperative as an oral dose and intravenously at wound closure. The primary outcome was blood transfusion rate. Further analysis on patient characteristics (e.g. age, gender), blood loss, perioperative haemoglobin (Hb) levels and complication/readmission rate was performed.

A total of 49 (0.9%) patients received perioperative allogenic blood transfusions. Mean age, distribution of gender, body-mass index, American Society of Anaesthesiologists score, duration of surgery, type of arthroplasty, estimated blood loss, perioperative Hb levels and length of stay were statistically significant different between transfused and not-transfused patients. The incidence of thromboembolic adverse events (e.g. deep vein thrombosis/lung embolism) was 0.5%. Low blood transfusion rate was found after implementation of a standardized perioperative TXA protocol for primary hip and knee arthroplasty.

Keywords : Tranexamic acid ; fast-track surgery ; knee arthroplasty ; hip arthroplasty ; unicompartmental knee arthroplasty.

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INTRODUCTION

Since the introduction of tranexamic acid (TXA) usage in primary hip- and knee arthroplasty procedures, perioperative blood loss is reduced with a decreased incidence of allogenic blood transfusions *(1,7,15,27,30)*. TXA is a synthetic analogue of the amino acid lysine that reduces blood loss by inhibiting the degradation of fibrin and disintegration of blood clots. Perioperative allogenic blood transfusions are strongly related to increased risk of surgical site infection and deep venous thrombosis *(14,17)*. Therefore, it is of paramount importance to prevent blood transfusions. Standardized perioperative protocols are used without an increased risk of

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perioperative thrombo-embolic events (e.g. deep venous thrombosis/pulmonary embolism) *(8,9,10,19)*. Given these benefits, a perioperative TXA protocol is increasingly implemented and used in primary hip and knee arthroplasty. Different perioperative protocols exist on type of administration, frequency of administration, dosage and timing of administration. TXA can be administered orally, intravenously or topical, with equal safety and efficacy in terms of postoperative blood transfusions and (low) adverse events (AE) rates *(2,3,8,10,11,19,21,28,29)*. To maximise the effect of TXA and minimise AE rates, perioperative protocols are needed with substantial clinical evidence. The aim of this study was to evaluate the incidence of perioperative allogenic blood transfusions after the implementation of a combined low-dose oral and intravenous TXA protocol for elective hip and knee arthroplasty.

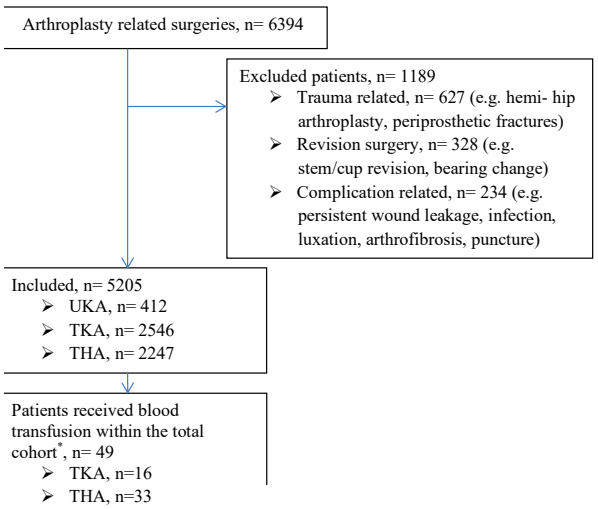

Figure I. — Patient selection process.
UKA, unicompartimental knee arthroplasty ; TKA, total knee arthroplasty ; THA, total hip arthroplasty ; *none of the UKA patients received allogenic blood transfusion.

PATIENTS AND METHODS

This retrospective cohort study evaluates the incidence of allogenic blood transfusions in patients who have been operated on primary total hip (THA), unicompartimental (UKA)- and total knee arthroplasty (TKA). All data was obtained from the hospital transfusion and surgery registration. To evaluate possible inclusion in this study, the complete database of surgeries performed between June 2014 and June 2019 were screened. All primary unilateral THA, UKA and TKA patients were included. Arthroplasty surgeries related to complications, revision or trauma were excluded from analysis. Selection of patients is presented in figure I.

All patients were operated with the use of standardized perioperative protocols regarding fast-track or outpatient surgery (e.g. multimodal pain management, mobilisation <24hrs after surgery, no drain/urinary catheter) *(22)*. In UKA procedures, tourniquet was used. Only in knee arthroplasty patients, local infiltration analgesia was used. Patients were either operated in the inpatient pathway, with an average length of hospital stay of 2 days, or as an outpatient with discharge from the hospital on the day of surgery *(18)*. Blood typing and cross matching was performed preoperatively in all patients. Patients were screened for preoperative anaemia and if deemed necessary, further analysed preoperatively in our hospital. Operations were performed under general or spinal anesthesia (with or without sedation). All patients received antibiotic prophylaxis (intravenous (IV) administration of 2000mg (<100 kg) ; 3000mg (>100 kg) Cefazolin) in three doses ; 15-60min before incision, 8 and 24hrs postoperative. In case of a known allergy for Cefazolin, Vancomycin (IV administration of 1000mg (<100 kg) ; 1500mg (>100 kg), preoperative dose and 12hrs postoperative second dose) was given. For patients following the outpatient pathway, the last dose was not given due to practical consideration.

TXA was given in two doses. First dose was given orally (Cyclokapron®, Mylan, Hatfield, United Kingdom) 2hrs before incision by the nurse on the orthopaedic ward. Second dose was given IV (Cyclokapron®, Pfizer, New York City, United States) at the end of the surgery when the wound was closed, administered by the anaesthesiology assistant. The dosage, orally and intravenously, depended on the weight of the patient ; <100kg : 1000mg, >100kg : 1500mg. In case of a known

hypersensitivity for TXA, severe renal function disorders (<50 mL/min creatinine clearance or dialysis depending) or recent history (<6 months) of a vascular event (e.g. cerebrovascular/myocardial infarction or deep venous thrombosis/pulmonary embolism), TXA was not given.

Postoperatively, all patients received thrombosis prophylaxis with the use of low molecular weight heparin (LMWH), except for patients who were on vitamin K antagonists (VKA) or non-VKA oral anticoagulants (NOAC) prior to surgery. LMWH thrombosis prophylaxis (subcutaneous injection of 5000IE (Dalteparin®, Pfizer, New York City, United States) once daily started on the day of surgery and was continued up to six weeks after the arthroplasty.

After surgery patients were monitored at the Post Anaesthesia Cure Unit (PACU) for several hours, before being transferred to the orthopaedic ward. Postoperatively, haemoglobin (Hb) levels were determined the first postoperative day. Except for patients undergoing UKA surgery via the outpatient pathway, Hb levels were not routinely measured. In case of general unwell-being, Hb levels were determined. Depending on Hb levels and clinical evaluation of the patient by the orthopaedic ward physician, allogenic blood transfusion was considered according to the recent national guide-lines *(20)*.

Data collection was performed via the in-hospital registration system of blood transfusions and the patient's digital medical records.

The primary endpoint of this study was the incidence of blood transfusions in elective hip- and knee arthroplasty. As secondary outcomes, patients in the transfusion group were compared to patient in the non-transfusion group on the following variables : gender, side of surgery, age, body-mass index (BMI), American Society of Anaesthesiologists (ASA) classification, type of anaesthesia (spinal or general), duration of surgery (minutes), type of arthroplasty (THA, UKA or TKA), patient specific instruments (PSI) usage in TKA, cementation in THA, estimated blood loss, pre- and postoperative Hb levels and length of hospital stay (LoS). In addition, the incidence of postoperative thrombo-embolic events (e.g. deep venous thrombosis/pulmonary embolism, cerebro-vascular, myocardial) up to 3 months postoperatively was assessed in both groups.

This study was performed in compliance with the Helsinki Declaration of 1975, as revised in 2013 and was studied and approved by the IRB (METC Z, Heerlen, the Netherlands, IRB Nr. METCZ20190123) and conducted in accordance with the guidelines for Good Clinical Practice (GCP).

All statistical analyses were performed with the use of Statistical Package for the Social Sciences version 26.0 for windows (SPSS., Inc., Chicago, IL). Descriptive statistics are used to summarize data. Student's t-tests were performed on significant interactions between both groups. Chi-square test was used for categorical variables. A threshold for all statistical comparisons of p-value ≤ 0.05 was considered to be statistically significant. Data are presented as means with standard deviations, 95% confidence level (CI), frequencies (%) or medians with ranges.

RESULTS

A total group of 5205 patients were analysed. The incidence of perioperative blood transfusion was 0.94% (n=49). One patient (TKA) received blood transfusion during the operation, as the other patients received blood transfusion after surgery on the clinical ward. Study patients were divided into two groups, transfused- (BT) and non-transfused (non-BT) patients. Differences for patient demographics and perioperative outcome measures between BT and non-BT patients are presented in table I.

Patients in the BT group had significant ($P \leq 0.05$) higher ASA score (≥III), age, prolonged LoS, and lower BMI scores. No significant differences were found for type of anesthesia and side of surgery. Only in THA patients, the BT group had a longer duration of surgery, higher estimated blood loss and consisted of significantly more uncemented arthroplasties.

Pre- and postoperative Hb levels in THA and TKA patients were statistically significant different between BT and non-BT patients. Since there were no transfusions in the UKA group ; estimated blood loss, duration of surgery and perioperative Hb levels could not be sub-analysed. AE's and readmission

Table I. — Demographic data for non-transfused and transfused patients are presented as mean (SD) with 95% confidence interval [CI] or frequencies (%). A p-value of ≤0.05 was considered to be statistically significant different

	Non-transfused (n=5.156)	Transfused (n=49)	p-value
Patient demographics			
Gender, female	3140 (60.9)	39 (79.6)	**0.008**
Side of surgery, right	2779 (53.9)	24 (49.0)	0.492
Age[a]	69.0 (9.3) [68.8-69.3]	76.3 (10.2) [73.4-79.2]	**0.000**
BMI[b]	28.9 (5.0) [28.7-29.0]	26.1 (4.8) [24.7-27.5]	**0.000**
ASA classification, I/II/III/IV	788/3918/444/6	0/38/10/1	**0.000**
Anesthesia, spinal/general	3743/1413	36/13	0.891
THA/TKA/UKA	2206/2523/412	33/16/0	**0.001**
Duration of surgery[c], THA	0:59 (0:16) [0:58-0:59]	1:02 (0:19) [0:56-1:09]	**0.028**
Duration of surgery[c], TKA	1:04 (0:16) [1:03-1:05]	1:10 (0:25) [0:56-1:24]	0.133
PSI usage in knee arthroplasty	1481 (58.7)	7 (43.8)	0.221
THA uncemented/cemented/hybrid/reversed hybrid	1860/154/143/38	19/11/2/1	**0.000**
Blood loss[d], THA	362.3 (171.7) [354.4-370.2]	421.7 (263.2) [307.9-535.6]	**0.024**
Blood loss[d], TKA	261.5 (119.1) [256.1-266.8]	323.1 (123.5) [248.4-397.7]	0.262
Pre-OR Hb level[e], THA	8.7 (0.8) [8.6-8.7]	7.2 (1.1) [6.8-7.6]	**0.000**
Post-OR Hb level[e], THA	7.3 (0.9) [7.2-7.3]	5.7 (0.7) [5.4-6.0]	**0.000**
Pre-OR Hb level[e], TKA	8.7 (0.8) [8.7-8.8]	7.3 (1.2) [6.6-7.9]	**0.000**
Post-OR Hb level[e], TKA	7.4 (0.8) [7.4-7.5]	5.5 (0.7) [5.1-5.8]	**0.000**
Delta Hb level[e], THA	1.4 (0.6) [1.3-1.4]	1.5 (0.8) [1.3-1.8]	0.873
Delta Hb level[e], TKA	1.3 (0.6) [1.2-1.3]	1.8 (1.2) [1.2-2.4]	**0.000**
Length of stay[f]	2.5 (2.0) [2.5-2.6]	5.4 (4.1) [4.3-6.6]	**0.000**

THA, total hip arthroplasty ; TKA, total knee arthroplasty ; UKA, unicompartimental knee arthroplasty ; ASA, American Society of Anaesthesiologists ; PSI, Patient Specific Instruments ; [a] presented in years ; [b] BMI : body-mass index is presented in kg/m^2 ; [c] presented in minutes ; [d] presented in mL ; [e] Hb, hemoglobin levels were presented in mmol/L ; [f] presented in days.

rates are presented in table II for both groups with an incidence of 0.46% for thromboembolic AE's (e.g. deep vein thrombosis/lung embolism/ cerebrovascular- or myocardial event).

DISCUSSION

The most important finding of the present study is that the use of TXA in primary hip- and knee arthroplasty results in low allogenic blood transfusion rates. Before implementation of TXA in hip- and knee arthroplasty, allogenic blood transfusion rates rose to more than half of the patients *(9)*. These transfusion rates decreased significantly by implementing a perioperative TXA protocol without increasing perioperative complications (e.g. thromboembolic, cardiovascular events) *(19,10,11)*. Different protocols are examined and

Table II. — Adverse event and readmission rates for the total cohort presented as frequencies (%)

	Total
Embolism (VTE/LE)	15 (0.29)
Neurologic (e.g. CVA, TIA)	7 (0.13)
Infection (e.g. surgical site infection)	23 (0.44)
Wound related (e.g. persistent drainage, dehiscence, haematoma)	79 (1.5)
Prosthesis related (e.g. dislocation, periprosthetic fracture)	74 (1.4)
Cardiac (e.g. acute myocardial infarction, acute heart failure, rhythm disorder)	16 (0.3)
Urologic (e.g. postoperative urinary tract infection, urinary retention)	191 (3.6)
Other (e.g. organ infection/dysfunction, nerve lesion)	77 (1.5)
Readmissions <3mnd post OR	262 (5.0)

VTE, venous thrombo embolism ; LE, lung embolism ; CVA, cerebrovascular accident ; TIA, transient ischemic attack.

proven to be effective and safe *(3,8,10,11,19,21,29)*. Nevertheless, none of these regimens regarding type of administration (e.g. topical, IV and oral), dosage and timing is superior *(10)*. In previous high-quality studies (e.g. meta-analysis) different types of administration resulted in similar decreased transfusion risks for TKA and THA patients (*11,27,30)*. Only in TKA patients, slight superiority is found for pre-incisional administration of IV TXA *(11)*. In terms of safety, multiple doses induce a prothrombotic state but do not provoke thrombosis in TKA and THA patients and would therefore be safe to use *(28)*. But, as known from the recent literature, a second or extended dose seems not to be more effective than single dosage in knee or hip arthroplasty *(11)*. No differences were found between low (<20mg/kg) and high (>20mg/kg) dose intravenous TXA in hip and knee arthroplasty *(11)*. As well as for timing of administration, no regimen is superior *(2,11)*.

The protocol in this study was set-up to be firstly evidence based, but secondly manageable without any nuisance for the patient. Due to the current fast-track protocols, which include 2hrs preoperative oral administration of pain medication, the implementation of preoperative oral TXA was done at that same administration time. When looking closely to the pharmacokinetics and pharmacodynamics of TXA, oral uptake is rapid, which makes oral TXA eligible. Bioavailability of TXA is approximately 45% in a healthy population, therefore a preoperative high dose of oral TXA can be considered to maximise the intraoperative blood sparing effect. T-max of TXA was estimated to be around 3 hours, in which the oral dose would almost be maximum at time of incision. Equal timeframe is stated for the elimination half-life of TXA. Therefore, the IV administration at the end of the surgery provides coverage for the first postoperative hours. These first 4 hours postoperative were stated by Jung et al. [16] to be most crucial in postoperative blood loss after knee arthroplasty.

A topical dose was not considered due to the use of local infiltration analgesia in TKA patients. Thereby, an addition of TXA would result in a high fluid volume which would be infiltrated in the surrounding knee tissue.

Various IV doses are used, with similar blood transfusion results *(21,27,29,30)*. Doses above 20mg/kg are considered to be a 'high dose'. Thus, in the presented study, a low dose oral and IV TXA was used which led to low blood transfusion rates. These results are in line with previous studies and would support a low dose TXA usage to prevent for drug side effects *(11)*.

The BT group consisted of significant more females. Other studies report female gender to be a risk factor for perioperative blood transfusion *(12,25)*. The exact mechanism remains unclear, but several hypotheses (e.g. lower preoperative haematocrit level and smaller body habitus) exists *(23)*. BT patients were significantly older and had a higher ASA classification, in line with previous findings *(12,23)*. This could be explained by the fact that in this group, blood transfusion was considered more often due to comorbidity status. On the other

hand, the decision for blood transfusion was not only based on ASA classification, but also strongly dependent on postoperative Hb levels and the clinical well-being of the patient. Since different thresholds for Hb levels were used, the transfusion rate could be biased. Nevertheless, BT patients had significant lower Hb levels preoperatively which can be seen as a risk factor for transfusion. Basora et al.[4] reported similar results regarding preoperative Hb level (7.7 mmol/L) and ASA classification (III-IV) in transfused TKA patients. A cut-off value for preoperative optimization was not given, but based on these and our results, preoperative Hb level seems to play a role in postoperative blood transfusion and should therefore be monitored preoperatively which was also found by other studies *(4,25)*. Unsurprisingly the BT group consisted of more THA patients, since blood loss in THA is higher and therefore significant higher risk for blood transfusion *(23,24)*.

In uncemented procedures more blood transfusions were given. In contrast to our results, Trice et al. *(26)* found no differences between a small cohort of uncemented and cemented/hybrid THA patients. Possible explanation for our results could be the opening of the intra-medullar canal, which is directly covered after cementation of the prosthesis in cemented THA. In the current cohort, uncemented THA was the preferred operation technique, even for patients with a higher age and thus relatively higher comorbidity status, which could have biased the results. To our knowledge, no clear evidence exists on the underlying mechanism.

No difference in anaesthesia method was found between BT and non-BT patients. In contrast to previous results, which have shown that spinal anaesthesia protects against allogenic blood transfusions *(13,23)*. Spinal anaesthesia decreases blood loss based on a reduction in sympathetic tone and blood flow to the operative extremity *(23)*. But these results were found in studies before implementation of TXA which makes it less comparable to the presented study. In most of the high-quality TXA studies, no data is provided.

There is of course a relation between duration of surgery and amount of blood loss with a self-evident increased transfusion risk *(12)*. Duration of surgery was previously described by Song et al. *(25)* as an independent risk factor for blood transfusion in THA patients. These results were obtained from arthroplasty surgeries with duration longer than 2 hours and only in THA patients *(25)*. For TKA patients, no significant difference was found. This is in line with our results. Although we found a significant longer duration of surgery in blood transfused THA patients, mean time between both groups was merely three minutes. The clinical relevance of three minutes is doubtful in our opinion.

Carling et al. *(6)* found low BMI to be associated with an increased risk of excessive blood loss and thereby increased risk for blood transfusion. In line with these results, our study found that BMI was significant lower in the BT group. Contrarily, other studies reported no difference or even significant more blood loss in obese patients *(5)*. The current evidence is divided on the role of BMI in blood transfusion risk after arthroplasty surgery. In this study we can't give more clarification on this topic and further studies are thus needed.

There are some potential limitations. Due to the retrospective nature of the study, presented perioperative complications (in particular vascular/hematologic) could possibly be underestimated. Data in this study depends on the registration of complications in our hospital system. On the other hand, similar (low) rates of thrombo-embolic events were found after the implementation of high-dose TXA in other studies *(8,9,19,28)*. In advantage of these results, the current protocol consists of a low-dose TXA protocol and should therefore be safe to implement in daily practice. Another possible limitation of the study is the lack of correction for anti-coagulant usage. This could potentially bias the blood transfusion rates due to the negative influence on perioperative blood loss.

CONCLUSION

Substantiated among with high-quality trials, TXA use in primary hip and knee arthroplasty holds an indispensable role in the perioperative process. As presented in this retrospective cohort study, an oral and IV administration protocol of TXA was found to be effective and safe for primary hip and knee arthroplasty procedures.

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