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ORIGINAL STUDY

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The addition of oral Tranexamic acid to knee arthroplasty patients does not further improve blood loss: a double blinded randomized control trial

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Perioperative intravenous (IV) TA has become routine in knee and hip arthroplasty. Less evidence exists on the administration of oral TA in the post-operative period. Our study aims to identify the efficacy and safety of combined perioperative IV and post-operative oral TA on blood loss and Hemoglobin (Hb) drop compared to perioperative IV TA alone.

Patients undergoing primary elective knee arthroplasty at our institution were invited to participate in the study (n=50). A computer-generated randomisation sequence was created online (www.randomization.org), with an allocation ratio of 1:1 and a block size of 50. Group A received perioperative IV TA alone and post-operative oral TA (n= 26) and Group B received perioperative IV TA plus 48 hours additional oral placebo (n= 24). Day 3 total blood loss and Hb drop was calculated. Continuous, normally distributed data (total blood loss) was compared utilising using one-way analysis of variance with post hoc Tukey test. Continuous skewed data (Hb drop) was compared using the Kruskal-Wallis test. P <0.05 was considered statistically significant. Group A demonstrated a trend in decreased total blood loss that was close to statistical significance (p = 0.072). No difference in Hb drop was identified between the 2 groups. Increased nausea was also observed in Group A. The administration of oral TA to post-operative knee arthroplasty patients does not improve further blood loss compared to patients receiving perioperative IV TA pre-operatively and at wound closure.

Keywords: Total knee replacement; total knee arthroplasty; blood loss; haemoglobin.

Abbreviations

TA	Tranexamic acid
Hb	Hemoglobin
IV	Intravenous
DVT	Deep venous thrombosis
PE	Pulmonary embolus
TKA	Total knee arthroplasty
PCI	Percutaneous coronary intervention
CR	Cruciate retaining
BMI	Body mass index
ASA	American society of anesthesiology

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INTRODUCTION

Total knee arthroplasty (TKA) has been associated with a considerable perioperative blood loss *(1,2)* and considerable efforts have been made to determine means of reducing it. Tourniquets are routinely used to minimize intraoperative bloods loss, although there are advocates for tourniquet-less knee arthroplasties. For procedures under tourniquet, blood loss associated with the operation occurs post desufflation *(3)*. Post-operative blood loss is further accentuated by fibrinolysis, as a combined consequence of surgical trauma and tourniquet application *(4)*.This fibrinolytic period can last 18-20hr following surgery *(4)*.

Large intraoperative and post-operative blood loss may result in requirement for allogenic blood transfusion and subsequent transfusion-related morbidity; decreased rehabilitation capacity; and increased length of hospital stay *(1,2)*. Minimizing blood loss is thus an important parameter in improving patient outcomes following surgery. Antifibrinolytic drugs such as Tranexamic acid (TA) have been shown to be efficacious in achieving this goal *(5,6,7)*.

TA is an artificial synthetic lysine derivative that competitively inhibits the activation of plasminogen into plasmin by blocking the lysine-binding sites of plasminogen to fibrin, which in turn inhibits the fibrinolysis process. It has a half-life of approximately 2-3 hours *(9)*. Administration can be intravenous, topical or oral, each with different cost profiles *(9)*. The timing of administration tends to be pre or peri-operatively. Topical administration is intra operative.

Few studies to date have identified the extended administration of supplemental oral TA in the post-operative knee arthroplasty patient *(5,6,7)*. The primary outcome of our study aims to identify the efficacy of combined perioperative IV and post-operative oral TA on blood loss compared to perioperative IV TA alone. The secondary outcome of our study aims to identify the efficacy of combined perioperative IV and post-operative oral TA on Hemoglobin (Hb) drop compared to perioperative IV TA alone. Further secondary outcomes aim to identify the safety profile of combined perioperative IV and post-operative oral TA administration compared to perioperative IV TA alone.

METHODS AND MATERIALS

This single-surgeon prospective randomized control trial was approved by the Products Regulatory Authority, Ireland (HPRA), and performed in our local Orthopaedic institute Midlands Regional Hospital, Tullamore, Ireland. Institutional ethical approval was attained and was further registered in the European clinical trials database (EudraCT) (no. 2017-002403-96). All patients 18 years of age or older who were scheduled for a primary total knee arthroplasty for severe symptomatic osteoarthritis were eligible for inclusion. Exclusion criteria included patients under 18 years of age, revision arthroplasty, bilateral arthroplasty, complex knee prosthesis, perioperative fracture, pregnancy, breast-feeding patient, history of thrombus or embolus, percutaneous coronary intervention (PCI) with stenting, and severe renal impairment. Informed consent was obtained from all recruited patients.

A computer-generated randomisation sequence was created online (www.randomization.org), with an allocation ratio of 1:1 and a block size of 50. One surgeon was responsible for enrolment of participants with dedicated screening occurring in the clinic setting. Following enrolment, further research personnel reconfirmed the inclusion and exclusion criteria of the patients. All participants were subsequently assigned a randomization number, with said numbers concealed into consecutively numbered sealed envelopes. Envelopes were subsequently opened on the morning of operation, and a research resident (who was not otherwise involved with the surgery or data collection) handled all the study drug materials; ascorbic acid and oral TA, to ensure similar appearances and blinding. This information was henceforth saved to an encrypted database. This information was subsequently used for collection and analysis by our independent research resident. The patients, surgeons, anaesthesists, data collectors, research residents, and outcome assessors were blinded.

Group A (oral TA group) received routine pre-operative intravenous TA (15mg.kg^{-1}) 30 min prior to tourniquet insufflation with a further second dose as described above. Furthermore, post-operative oral TA (1g three times a day) was administered, which commenced 8 hours following surgery for a duration of 48 hours following completion of surgery.

Group B (oral placebo group) received routine pre-operative intravenous TA (15mg.kg^{-1}) 30 min prior to tourniquet insufflation with one further dose of (15mg.kg^{-1}) IV given on wound closure initiation. No further post-operative TA was administered. Placebo oral ascorbic acid (500mg three times daily) was administered to Group B participants postoperatively for blinding purposes (commencing 8 hours following surgery for a duration of 48 hours following completion of surgery).

To help prevent labile hematocrit analysis, maintenance hourly IV fluids specific to each participants' body mass were prescribed immediately post-operatively (4mL.kg^{-1} for first 10kg body mass, 2mL.kg^{-1} for 2nd 10kg body mass, and 1mL.kg^{-1} for the remaining body mass). Maintenance IV fluids lasted for 16 hours following completion of surgery with strict supervision of oral intake.

All total knee arthroplasties were performed by, or under direct supervision of, the senior surgeon. All patients had a spinal anesthetic. All procedures were performed via a midline incision, medial parapatellar approach and with a measured resection technique. Intramedullary guides were used for all femoral preparations, and extramedullary guides were used for the tibial preparation. A cemented cruciate retaining (CR) design was utilized (Triathlon®; Stryker Orthopaedics, Mahwah, NJ USA)) with a modular tibial baseplate. Tourniquet application occurred for each patient at a pressure of 350mmHg and insufflated following application of an Esmarch bandage. Insufflation occurred prior to incision and was released following wound closure. No wound drains were placed. All patients received a uniform periarticular intraoperative injection consisting of 150mL 0.25% bupivacaine, morphine 0.5mg and 1mL 1:1000 adrenaline. Intraoperative electrocautery for hemostasis was used. Intra-operative blood loss volume was recorded.

Following surgery, patients were monitored in in post-anesthesia care unit until fit for ward transfer. Routine vital sign assessment take place for each participant. Physiotherapy assessment would take place the day of surgery with follow up daily. All patients were allowed to fully weight bear with aid of frame or crutches following surgery. Mechanical and chemical venous thromboembolism prophylaxis was utilized for each participant: subcutaneous Enoxaparin sodium (Clexane® 40mg Aventis Pharma SA, France) coupled with intermittent compressive footwear (A-V Impulse™. Covidien ltd, Ireland) Enoxaparin was administered 10 hours following surgery as per local protocol and is continued every 24hr until discharge. Aspirin 150mg daily oral tablets were prescribed following discharge for a further duration of four weeks.

Patient demographic data and preoperative characteristics such as gender, BMI and age were recorded along with American society of anesthesiologist grade (ASA) and complication rate. Primary outcome measures involved estimated total blood loss from surgery. In the absence of intra articular wound drains, estimated total blood loss was calculated via the Gross formula *(10)*. Secondary outcome measures collected included Total Hb drop. Baseline pre-operative complete blood count including Hb (Hb_0) and Hct were collected and compared to day 3 postoperative Hb (Hb_1). Total Hb drop was calculated as Hb drop between day 3 Hb (Hb_1) and preoperative Hb (Hb_0) i.e. Hb_1 -Hb_0.

Further secondary outcomes measure included rate of blood transfusion as well as incidence of thromboembolic events or other sequelae that arose as a result of TA administration.

Sample size calculations were determined on differences in the estimated 72-hour blood loss volume. Previous literature has identified 72-hour total blood loss volumes of 1104 mL, with a standard deviation of 254 mL *(11)*. In this study we assumed a clinically important blood loss difference of 220 mL, which was equivalent to a reduction in blood loss of 20% in the aforementioned cohort. The sample size was calculated using a fixed-effect one-way analysis of variance, with an alpha level of 5% and a power of 90%. A minimum of 46 patients was required, 23 per group. Data was analysed using

Table 1. — Patient demographics and results.

	Combined IV + Oral TA Group (n= 26) Group A	IV TA + Oral Placebo Group (n =24) Group B
Age	66.4 +/- 13.9	63.9 +/- 10.4
Gender	17F, 9M	13F, 11M
BMI	30.1 +/- 4.7	29.9 +/- 6.2
ASA 1-2	26	24
Preoperative Hb	13.9 +/- 1.2	13.2 +/- 0.9
Preoperative Hct	0.4	0.4
Day 3 Hb	11.4 +/- 1.1	10.6 +/- 0.8
Day 3 Hct	0.3	0.3
Total Hb drop	2.5 +/- 0.8	2.6 +/- 0.4
Intra-operative blood loss	< 50mL	< 50mL
Total blood loss	833 +/- 405	1041.5 +/- 335
Transfusion rate	0	0

BMI = body mass index, F = female, M = male, ASA = American society of anesthesiology, Hb = haemoglobin, Hct = haematocrit, mL = millilitre.

SPSS, version 24 (IBM) and MedCalc for Windows, version 15.0 (MedCalc Software). The statistical power of the study was calculated using G-Power software (Version 3.1.9.2, Germany). Continuous, normally distributed data (total blood loss) were compared utilising using one-way analysis of variance with post hoc Tukey test with continuous skewed data (Hb drop) compared with using the Kruskal-Wallis and Nemenyi post hoc test. P <0.05 was considered statistically significant. P <0.05 was considered statistically significant.

RESULTS

In total, 55 patients were scheduled to receive a primary unilateral total knee replacement under care of the main author from January 2017 to June 2018. 5 patients were excluded from the study due to personal history of thrombus (2), embolus (1) and PCI with stenting (2). The remaining 50 patients were included with 26 patients randomized to the IV+ Oral TA group (Group A) and 24 patients randomized to the IV TA and oral placebo group {group B} (see Table 1).

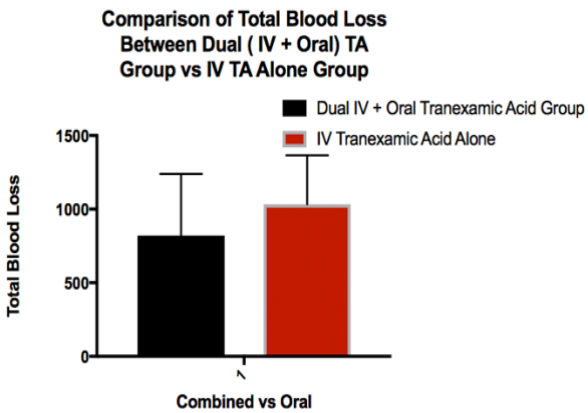

Fig. 1. — Total blood loss calculated for patients receiving both IV and oral Tranexamic acid combined versus IV tranexamic acid alone.

The total blood loss recorded for Group A (833 +/- 405) was lower than that recorded for Group B (1041.5 +/- 338), p = 0.072. No statistical significance was identified between the 2 groups, see Fig. 1.

The Hb drop in Group A (2.5 +/- 0.8) was almost identical to the Hb drop experienced by Group B (2.6 +/- 0.4), p = 0.58. There was also a similar

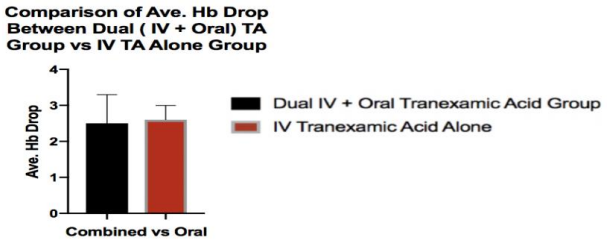

Fig. 2. — Average Hb reduction in patients receiving both IV and oral Tranexamic acid combined versus IV tranexamic acid alone.

drop in Hct in Group A (0.1) to Group B (0.1), p= 0.99. No differences in Hb or Hct drops were noted between the 2 groups, see Fig. 2.

No patient from either group required allogenic blood transfusion.

There were no thromboembolic events recorded in either Group throughout this study. Within the 24 patients in group B, 2 experienced gastrointestinal upset (severe nausea) on day 1 post op. 1 patient experienced an acute episode of atrial fibrillation which settled following appropriate medical input, see Table 2.

Table 2. — Complications per group

Complication	Oral TA Group (n = 26) Group A	Oral Placebo Group (n= 24) Group B
Deep Venous Thrombosis	0	0
Pulmonary Embolus	0	0
Gastrointestinal upset	2	0
Cardiovascular	1	0
Wound issues (Stitch sinus)	1	0
Blood Transfusion	0	0

DISCUSSION

Our study aims to establish the effect on blood loss between two regimes of dosing of TA, with the addition of PO TA postoperatively in our treatment group compared to single dose pre-operative in the control group. Group B received six post-operative doses of oral TA. We did not establish a difference in our primary outcome measure of total blood loss. Although there was a trend in decreased total blood loss, this did not reach statistical significance (see Table 1). Furthermore, secondary outcome assessment of Hb drop was recorded as almost identical between Group A and Group B (see Table 1).

Whilst the efficacy in reduction in blood loss from the utilization of TA is well established, the optimum dose, timing, and administrative modality is still subject to multiple studies across the literature *(5,6,7,12)*. Oral TA has the benefit of ease of administration compared to IV or intra-articular (IA) forms and is economically favorable *(9)*. Oral TA has been shown to be as efficacious as IV when given pre-operatively *(9,13)*. Oral TA has a bioavailability of 34%, therefore a dose of 1g TDS will equate to receiving 1g IV TA *(8)*. This dose is in concordance with authors Lee et al. *(14)* and Zohar et al. *(15)*.

Periods of fibrinolysis can occur for up to 18 hours following surgery *(4)*. TA has a half-life of 3 hours *(8)*. Administration of TA pre-operatively may not cover the extended fibrinolytic period experienced by patients. The further administration of TA at wound closure or perioperatively has been shown to have further blood sparing effects in hip arthroplasty *(16)*. This has been shown to be true for both IV and oral TA *(5,6,12)*. Further post-operative TA may help offset the hyper-fibrinolytic period experienced by patients. Few studies have assessed the extended administration of post-operative TA to patients compared to routine perioperative TA. The majority of literature currently available focuses on the perioperative period with little evidence existing examining the extended effect of oral Tranexamic acid in the post-operative period.

Recently, Wang et al. *(7)* compared the effects of the addition of post-operative oral TA at 3 hours (Group B), 9 hours (Group C) and 15 hours (Group D) to pre-operative oral TA alone (Group A) *(7)*. In this RCT, the patients receiving 2 and 3 post-operative oral doses of TA had a statistically significant lower blood loss compared to the groups receiving one post-operative dose or no post-operative dose. Wang et al. found no difference

between the groups receiving 2 and 3 post-operative doses. Total blood loss was calculated from formulae outlined by Nadler et al. *(17)* and Gross et al. *(10)* which are reliant on Hct.

Charoencholvanich et al. *(12)* compared peri-operative IV TA coupled with 5 days of oral post-operative TA to control group alone. Here, a statistically significant reduction in blood loss and Hb drop was identified. No perioperative IV group existed in this study. It is likely that the 5-day period of oral TA was not required to elucidate a major decrease in total blood loss compared to IV perioperative alone. We know from more recent literature that perioperative IV TA and oral TA are both similar in blood-sparing efficacy *(9,13)*. Although 2 and 3 doses of post-operative oral TA have been shown to decrease total blood loss and Hb drop *(7)*, we believe the second dose of IV perioperative TA in our study offset the effects of the post-operative oral TA. Furthermore, we feel a relative strength of our study was a carefully matched fluid regimen for each patient based on their body mass. This helped prevent a potentially labile Hct reading. Such a fluid maintenance regimen was not stated in the previously cited studies *(7,12)*.

While oral tranexamic acid has shown to be more cost effective than IV in administration *(9)*, assessment of side-effects induced as a result of oral ingestion may not be comparable. In our study, 2 patients receiving oral TA had severe GI nausea and upset. Surgical input out-ruled any organic cause for same. It is possible that the addition of oral TA contributed to these symptoms, although difficult to quantify given the low numbers in the study. Although this particular side-effect has not been identified in orthopedic literature to date, authors have identified a 12% incidence of nausea and vomiting in patients taking oral TA for menorrhagia *(18)*. This high rate of aforementioned nausea was present at a similar oral dose (1g four times daily) to our study.

Prolonged anti-emetic treatment was required to help alleviate these symptoms and resulted in delayed rehabilitation post-operatively. Furthermore, from a pragmatic point of view, the administration of oral TA 2 hours pre-operatively for a patient who is first on the list may not always be possible. In this circumstance the administration of IV TA 30 min prior to surgery is the preferred option.

In this study, there was no increase in adverse VTE events within the group receiving post-operative oral TA. No patients in our study suffered from a DVT or PE. One patient in the combined group had atrial fibrillation immediately in the post-operative period which settled with appropriate medical management. It is unlikely that the administration of TA had incurred this event. This is comparable with other authors who have found similar safety profiles with TA administration *(14)*.

There are several limitations to the study we have performed. Firstly, power analysis incorporated in our study was calculated based on blood volume loss of 220mL. Although there was a trend in decreased total blood loss, a larger patient cohort may be required to elucidate statistical significance for same. Furthermore, total blood loss in our study was calculated on day 3 Hct. It is possible that day 4 or 5 full blood count levels may have identified a further Hb drop or further blood loss.

CONCLUSION

The administration of oral TA to post-operative knee arthroplasty patients does not add further blood sparing efficacy compared to patients receiving perioperative IV TA pre-operatively and at wound closure. Post-operative oral TA does not incur additional thromboembolic risks to patients undergoing knee arthroplasty.

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