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ORIGINAL ARTICLE

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Oral as compared to intravenous tranexamic acid to limit peri-operative blood loss associated with primary total hip arthroplasty

A randomised noninferiority trial

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BACKGROUND Oral as compared to intravenous tranexamic acid (TXA) is an attractive option, in terms of cost and safety, to reduce blood loss and transfusion in total hip arthroplasty. Exclusion criteria applied in the most recent randomised trials may have limited the generalisability of oral tranexamic acid in this indication. Larger and more inclusive studies are needed to definitively establish oral administration as a credible alternative to intravenous administration.

OBJECTIVES To assess the noninferiority of oral to intravenous TXA at reducing intra-operative and postoperative total blood loss (TBL) in primary posterolateral approached total hip arthroplasty (PLTHA).

DESIGN Noninferiority, single centre, randomised, double-blind controlled study.

SETTING Patients scheduled for primary PLTHA. Data acquisition occurred between May 2021 and November 2022 at the University Hospital of Liège, Belgium.

PATIENTS Two hundred and twenty-eight patients, randomised in a 1 : 1 ratio from a computer-generated list, completed the trial.

INTERVENTIONS Administration of 2 g of oral TXA 2 h before total hip arthroplasty and 4 h after incision (Group oral) was compared to the intravenous administration of 1 g of TXA 30 min before surgery and 4 h after incision (Group i.v.).

MAIN OUTCOME MEASURES TBL (measured intra-operative and drainage blood loss up to 48 h after surgery, primary outcome), decrease in haemoglobin concentration, D-Dimer at day 1 and day 3, transfusion rate (secondary outcomes).

RESULTS Analyses were performed on 108 out of 114 participants (Group i.v.) and 104 out of 114 participants (Group oral). Group oral was noninferior to Group i.v. with regard to TBL, with a difference between medians (95% CI) of 35 ml (-103.77 to 33.77) within the noninferiority margins. Median [IQR] of estimated TBL was 480 ml [350 to 565] and 445 ml [323 to 558], respectively. No significant interaction between group and time was observed regarding the evolution of TBL and haemoglobin over time.

CONCLUSIONS TXA as an oral premedication before PLTHA is noninferior to its intravenous administration regarding peri-operative TBL.

TRIAL REGISTRATION European Clinical Trial Register under EudraCT-number 2020-004167-29 (https://www.clinicaltrialsregister.eu/ctr-search/trial/2020-004167-29/BE).

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KEY POINTS

- Tranexamic acid is recommended in total hip arthroplasty to limit peri-operative blood loss.
- Oral tranexamic acid offers safety and financial advantages as compared with the intravenous form.
- Oral administration is noninferior to intravenous administration regarding peri-operative bleeding in primary total hip arthroplasty.
- Oral should supplant intravenous tranexamic acid and be more widely used as a premedication.

Introduction

Total hip arthroplasty (THA) is associated with major bleeding and postoperative in-hospital anaemia occurs in approximatively 26% of cases.[1] Acute postoperative anaemia increases morbidity, mortality, length of stay and the frequency of heterologous blood transfusion.[2] Tranexamic acid (TXA) is an antifibrinolytic agent, widely used to reduce blood loss in THA.[3,4] The effectiveness and safety of TXA is well established, and this medication is strongly recommended as a second pillar of patient blood management (PBM) to decrease transfusion rate in THA.[5–8] Although the pharmacology and efficacy of oral TXA has already been studied in other settings (e.g. postpartum),[9] in prosthetic surgery, few trials have been conducted. Recent meta-analyses in 2019 and 2020 have highlighted the need for higher quality and larger size trials to evidence the oral administration of TXA as a credible alternative, given the heterogeneity of the studies included in these meta-analyses.[10,11] To demonstrate the reliability of this alternative, noninferiority trials should ideally be performed before superiority trials, which was not the case at the time we designed the present study. Given the high efficacy of intravenous (i.v.) TXA for preventing blood loss in THA, new studies on oral TXA should not be compared with placebo but with the i.v. form. In addition, the above-mentioned studies had a large number of exclusion criteria, including comorbidities such as atrial fibrillation, use of antiplatelets or anticoagulant drugs, and a history of myocardial infarction or stroke. This biases the recruitment of patients and limits the generalisability of results to the population concerned by THA, namely the elderly where the prevalence of such co-morbidities is high.[12] In addition to ease of administration, the oral route reduces the risk of medication administration errors. Depending on the definition of such errors, the incidence of these undesirable events, all routes combined, may be as high as 6.1%,[13] while the i.v. route has a misadministration risk of 10.1%.[14] Because of the immediate absorption and distribution into the circulation, adverse effects are more difficult to mitigate in the event of improper i.v. administration. These considerations highlight the value of oral drug use in terms of patient safety and pharmaco-economics, and provide a rationale for assessing the oral route in larger and more inclusive studies to definitively show it to be the best solution in THA.

Hence, the primary aim of our trial was to assess the noninferiority of oral as compared to i.v. TXA at reducing total blood loss (TBL), including intra-operative and postoperative blood loss up to 48 h after surgery in posterolateral approached THA (PLTHA), in a population of patients with the closest characteristics to real life, that is with the least restrictions to patient inclusion.

Secondarily, we aimed at statistically comparing the calculated TBL (CTBL) between groups of patients over time to support our primary outcome, as well as transfusion rates and the evolution over the first postoperative three days of several biological markers of importance with regard to blood loss. To document the TXA activities over time, the concentration of D-dimers as a marker of plasmin inhibition and C-reactive protein (CRP) as a control for the direct inhibition of the proinflammatory action of plasmin on the complement system were also measured and recorded.[15]

Our protocol was designed in accordance with the most comprehensive data about the bioavailability and pharmacokinetics of TXA.[16–18]

Materials and methods

Trial design

This prospective, randomised, clinical trial was approved by our Institutional Review Board (Comité d'Ethique Hospitalo-Facultaire Universitaire de Liège; President: Prof. V. Seutin; IRB number: 707) under the study number 2020/316 on 15 March 2021. Prior to patient enrolment, the trial protocol was registered in the European Clinical Trial Register under the EudraCT-number 2020-004167-29 (https://www.clinicaltrialsregister.eu/ctr-search/trial/2020-004167-29/BE) on March 15th 2021 (principal investigator: Piette Nicolas) and in the U.S. Clinical Trial Register under the identifier NCT04691362 (https://clinicaltrials.gov/study/NCT04691362). This study adheres to the applicable CONSORT guidelines and was performed in accordance with the most recent version of the Helsinki Declaration. Data acquisition occurred between 10 May 2021 and 6 December 2022 at the University Hospital of Liège, Belgium.

Participants

Patients scheduled for primary elective PLTHA under spinal or general anaesthesia were approached to be included in this study. The inclusion criteria were adults (>18 years of age) with ASA physical status I, II and III. Exclusion criteria were refusal to be included, known allergy to TXA or inability to understand the protocol. Other exclusion criteria were chronic kidney disease with serum creatinine more than 1.4 mg dl^{-1}, patients with

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thromboembolic disease during the last 12 months, patients with a history of bariatric surgery that could lead to malabsorption (e.g. sleeve, by-pass, gastrectomy, intragastric balloon), uncontrolled diabetes with potential gastroparesis, ongoing treatment with oral anticoagulants or double antiaggregation for whom pre-operative discontinuation according to the American Society of Regional Anaesthesia and Pain Medicine (4th edition 2018) recommendations could not be achieved, or patients in whom therapeutic anticoagulation with low-molecular-weight heparin (LMWH) should have been necessary before surgical drain removal (e.g. mechanical valve prosthesis). Aspirin alone was not discontinued in case of secondary prevention and was not an exclusion criterion.

Intervention

An individual package was prepared with a randomisation number which contained either eight anonymised and repackaged tablets of oral TXA 500 mg and two ampoules of normal saline 50 ml (Group oral), or eight tablets of placebo and two ampoules of normal saline 40 ml to which 10 ml of a TXA 100 mg ml^{-1} solution had been added (Group i.v.). The ward nurse was instructed to give the oral premedication at the patient's bedside at 6 a.m. for the first case of the day or, following a telephone call from the operating theatre, about two hours before skin incision. All patients received four tablets of oral TXA (group oral) or placebo (group i.v.) as premedication. Fifty millilitres of the TXA (20 mg ml^{-1}; Group i.v.) or placebo (Group oral) solution were i.v. administered 30 min prior to skin incision in all patients at a rate of 200 ml h^{-1} in the operating room. As a second dose, the same i.v. solution (TXA in Group i.v. or placebo in Group oral) and the same four oral tablets (TXA in Group oral or placebo in Group i.v.) were administered to the patient four hours after skin incision by the ward nurse on the ward.

Anaesthesia and analgesia protocol

Patients received oral premedication including dexamethasone 24 mg and etoricoxib 60 mg 1 h before surgery. After peripheral venous catheterisation, a Hartmann's solution infusion was initiated, at a rate adjusted according to intra-operative blood loss. Surgery was performed under spinal or general anaesthesia. Multimodal analgesia techniques such as supra-inguinal fascia iliaca or pericapsular nerve groups block were conducted according to the most recent guidelines,[19] with postoperative acetaminophen 1 g 6 hourly and etoricoxib 60 mg 24 hourly. Sublingual tramadol and oxycodone were used for rescue analgesia.

Surgical protocol

Surgery was performed using a posterolateral approach according to Moore.[20] At the surgeon's discretion, some patients had a cemented femoral stem. A single drain was placed in contact with the joint capsule and was removed 48 h after surgery. Thromboprophylaxis with LMWH, enoxaparin 40 mg 24 hourly, was prescribed, starting 6 h postoperatively and then continued once a day at 8 p.m. Antibiotic prophylaxis was achieved using i.v. Cefazolin 2 g at least 30 min before skin incision.

Outcomes

The primary outcome of the study was the noninferiority of oral TXA when compared with i.v. TXA with regard to TBL occurring intra-operatively and during the first 48 h after surgery (intra-operative blood loss and collected blood loss in drain up to day 2). Secondary outcomes included transfusion rate, the evolution of TBL and CTBL at the different time points of recording. Blood sampling was performed pre-operatively as well as on day 1 and day 3, to monitor the evolution of CTBL during first 3 days after surgery according the Camarasa formula (Fig. 1),[21,22] haemoglobin level, haematocrit, platelet count, creatininaemia, glomerular filtration rate according to the Cockcroft-Gault formula, INR, fibrinogenaemia, D-dimer concentration and CRP. Transfusions were recorded throughout the hospital stay and a restrictive strategy was adopted with a threshold of haemoglobin concentration for transfusion set at 7 g dl^{-1}. The time of TXA/placebo administration was also recorded to determine whether the administration was consistent with the protocol and pharmacology with a 99% confidence interval (99% CI).

Sample size

The noninferiority margin for rejecting the null hypothesis was set at 164.4 ml of TBL, corresponding to 20% of a

Fig. 1 Camarasa formula.

$$\text{TBL (ml)} = \frac{\text{TRCL (ml)}}{\text{mean Hi-Hf}}$$

Note:

TRCL = ARCL + VTRC (ml); ARCL = Vth x (Hi-Hf); Vth in men = weight (kg) x 70; Vth in women = weight (kg) x 65

TBL = total blodd loss; TRCL = total red cell loss; Hi haematocrit before surgery; Hf = haematocrit 3 days after surgery; ARCL = accepted red cell loss; VTRC = volume of transfused red blood cells; Vth = estimated blood volume (ml)

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presumed TBL of mean 800 ml (SD 356), as estimated using a sample of data from our institutional database. Accordingly, 198 patients were needed to reach 90% power with an alpha threshold of 0.025, using a one-sided Wilcoxon-Mann-Whitney *U* test for unrelated samples. Assuming a drop-out rate of 15% after randomisation, 228 patients were planned for recruitment and randomisation at a 1 : 1 ratio.

Randomisation and blinding process

After thorough explanations on the study rationale by the principal investigator (NP), written informed consent was obtained prior to inclusion of eligible patients into the trial. Following the 1 : 1 ratio, patients were enrolled using a computer-generated randomisation list into two groups and an individual closed bag was assigned to patients according to their recruitment order. Bags were prepared by clinical pharmacist who packaged drugs and placebo. The anaesthesiologists, surgeons, nurses and patients were blinded as to drugs preparation and administration. The blinded anaesthesiologist noted the intraoperative blood loss in the suction reservoir at the end of surgery and the ward nurses noted blood content in the surgical drain at postsurgical day 1 and day 2, immediately before drain removal.

Statistical analyses

All statistical analyses and a priori sample size calculation were performed using the R package (version 4.2.2; R Foundation for Statistical Computing, Vienna, Austria).

Normality of distributions was tested whenever required by calculating the skewness of distributions and using the Shapiro–Wilk test. Demographic and nonrepeated measure data were compared between groups using Fisher's exact tests, χ^2 tests, Wilcoxon-Mann-Whitney or two-tailed Student's unpaired *t*-tests as appropriate. For the noninferiority assessment regarding TBL, the 95% CI of the median was calculated using the Huber sandwich estimator method. We used generalised linear mixed model (GLMM) tests to analyse the evolution, during first 48 postoperative hours, of TBL, the evolution of CTBL at day 1 and day 3, and the evolution over time of all biological markers. For the mixed model, time, patient group and their interaction were defined as fixed effects, with time as a repeated-measure factor. The chosen covariance type was the variance components. The degrees of freedom were calculated using the residual method. A sequential Bonferroni correction was applied to adjust for multiple comparisons. A one-tailed *P* value less than 0.025 for the noninferiority analysis or a two-tailed *P* value less than 0.05 for analyses of secondary endpoints were considered statistically significant as appropriate.

Results

A total of 242 patients scheduled for elective PLTHA were screened for eligibility. After exclusion of 14 due to patient refusal (four patients) or not meeting all inclusion criteria (one patient ASA IV, two patients with creatinaemia higher than 1.4 mg dl^{-1}, two patients with previous bariatric surgery, one patient with uncontrolled diabetes, two patients with mechanical cardiac valve and two patients unable to understand the protocol), 228 patients were enrolled into the study and randomly assigned to one of the two study groups, with a 1 : 1 ratio. The allocation process according to CONSORT is presented in Fig. 2. Due to a loss of data (loss of the data collection sheet, or missing data on this sheet), 108 out of 114 participants (Group i.v.) and 104 out of 114 (Group oral) were included in the noninferiority analysis. Concerning secondary outcomes, following an intention-to-treat approach, we also analysed data from patients with missing data. This was possible thanks to the chosen methodology; GLMM analysis, which is a flexible model with respect to missing data. The number of patients whose data were included in each analysis can be inferred from the degrees of freedom (df) shown in the results and in the Appendix 1, http://links.lww.com/EJA/A911.

Demographic characteristics, antithrombotic therapy, times of TXA or placebo administration, type of anaesthesia, length of surgical procedure and surgical characteristics were similar between the groups (Table 1).

The time of TXA/placebo administration (99% CI) was -139 (-147 to -132) min before incision for the first oral dose and -24 (-26 to -23) for the first i.v. dose. Oral and i.v. second doses were administered 207 (192 to 217) min after incision (Fig. 3).

The between-group median difference in measured TBL (95% CI) was -35 (-103.77 to 33.77), $P < 0.001$, within the noninferiority margin, hence allowing the acceptance of the noninferiority hypothesis (see Additional Figure in the Appendix 1, http://links.lww.com/EJA/A911). Median [IQR] of measured TBL was 480 ml [350 to 565] in Group i.v. and 445 ml [323 to 558] in group oral. According to the GLMM analysis, measured TBL was not significantly different between groups at all time points of interest, with no significant main effect of group affiliation ($F_{(1,207)} = 0.948$; $P = 0.331$) or interaction between time and group ($F_{(2,311)} = 0.293$; $P = 0.682$) (Fig. 4).

Similarly, the groups did not differ regarding the evolution of CTBL. The median [IQR] of CTBL at day 3 was 859 ml [519 to 1133] in Group i.v. and 840 ml [583 to 1195] in Group oral ($P = 0.63$).

The incidence of allogenic transfusion was similar between groups ($n = 1$ or 0.9% in both groups). No adverse event related to the protocol was noted. No difference was observed for any of the other secondary outcomes; no main effect of group or interaction between time and group was noted for haemoglobin, D-dimer, haematocrit, fibrinogen, CRP, creatinine, glomerular filtration rate

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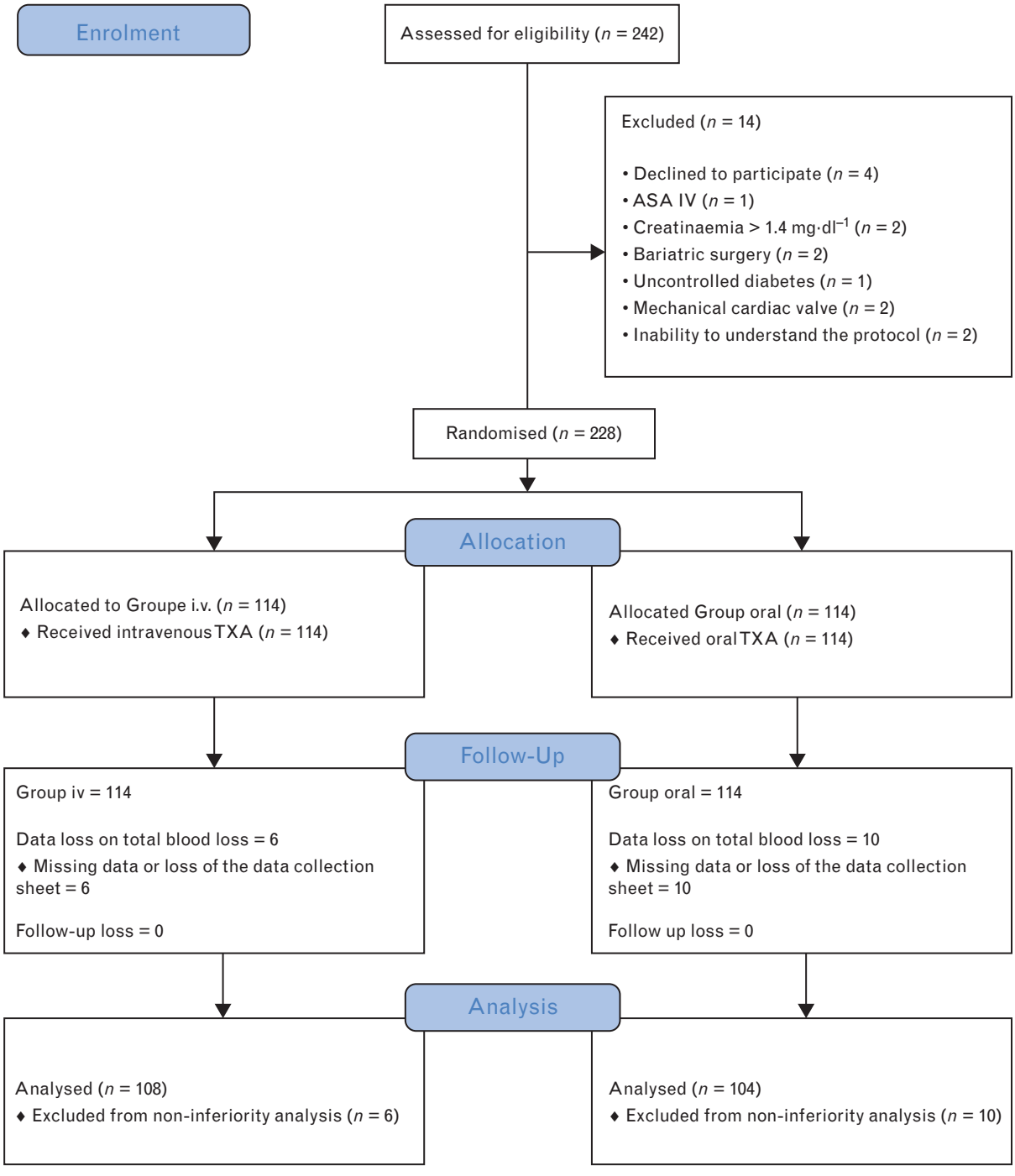
Fig. 2 CONSORT flow chart of patient enrolment, group allocation, follow-up and data analysis.



CONSORT, CONsolidated Standards Of Reporting Trials; Group i.v., patients having received intravenous tranexamic acid; Group oral, intervention group, patients having received oral tranexamic acid.

according to the Cockcroft-Gault formula (Appendix 1, http://links.lww.com/EJA/A911).

Discussion

The main finding of our study is the noninferiority of oral TXA as compared with i.v. TXA regarding peri-operative TBL. Our primary outcome is supported by the lack of differences between the groups over time regarding secondary outcomes such as CTBL, transfusion rate, haemoglobin and haematocrit, or markers of TXA activity such as CRP or D-dimers. Our results complement the conclusions of the recent meta-analyses mentioned in the

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Table 1 Demographic and surgical procedure characteristics

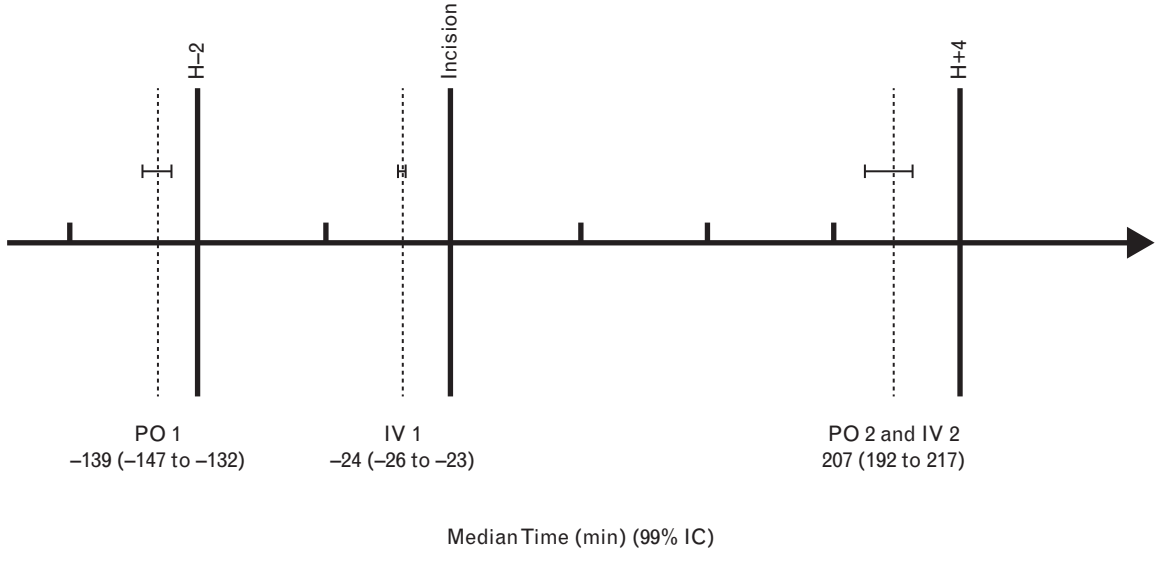
	Group i.v. $n = 114$	Group oral $n = 114$
Demographic characteristics		
Age, years; mean ± SD	67.04 ± 11.48	67.94 ± 11.40
Sex, *n* (%) women	66 (57.9)	72 (63.2)
ASA classification, *n* (%)		
I	10 (8.8)	4 (3.5)
II	86 (75.4)	97 (85.1)
III	18 (15.8)	13 (11.4)
Weight, kg; median [IQR]	78.00 [66.00 to 90.75]	74.00 [64.25 to 89.00]
Height, m; median [IQR]	1.68 [1.62 to 1.77]	1.65 [1.60 to 1.72]
BMI, kg m^{-2}; median [IQR]	26.80 [24.42 to 31.10]	26.70 [24.13 to 30.50]
Medical pre-operative conditions		
Lee's Score, *n* (%)		
0	89 (78.1)	88 (77.2)
1	25 (21.9)	23 (20.2)
2	0 (0.0)	2 (1.8)
3	0 (0.0)	1 (0.9)
Aspirin, *n* (%)	19 (16.7)	16 (14.0)
Diabetes, *n* (%)	19 (16.7)	23 (20.2)
Tobacco consumption, *n* (%)	17 (14.9)	23 (20.2)
Pre-operative Hb, g dl^{-1}; mean ± SD	13.95 ± 1.43	13.63 ± 1.49
Kockcroft-Gault, ml min^{-1}; median [IQR]	81.60 [65.20 to 104.10]	73.40 [58.30 to 100.20]
Anaesthetic characteristics		
Regional anaesthesia, *n* (%)	114 (100.0)	110 (96.5)
Spinal anaesthesia, *n* (%)	101 (88.6)	104 (91.2)
General anaesthesia, *n* (%)	16 (14.0)	12 (10.5)
Crystalloids, ml; median [IQR]	400 [200 to 600]	300 [200 to 600]
Surgical characteristics		
Duration of surgery, min; median [IQR]	68 [60 to 79]	67.5 [60 to 77]
Cement, *n* (%)	33 (28.9)	30 (26.3)

ASA, The American Society of Anesthesiologists physical status classification system; IQR, interquartile range; SD, standard derivation.

introduction of this article,[10,11] highlighting the need for additional clinical trials to evidence the oral administration of TXA as a credible alternative to the i.v. route.

Although another large concurrent randomised trial was conducted recently, and concluded that oral TXA in THA was noninferior to i.v. TXA, the authors conceded that some limitations, particularly concerning the large

Fig. 3 Timeline of the effective administration of tranexamic acid, with 99% confidence intervals (99% CI).



Note:
H-2 = 2 hours before incision; H+4 = 4 hours after incision; PO1 = first oral dose as premedication; IV1 = first intravenous dose; PO2 and IV2 = second oral and intravenous doses

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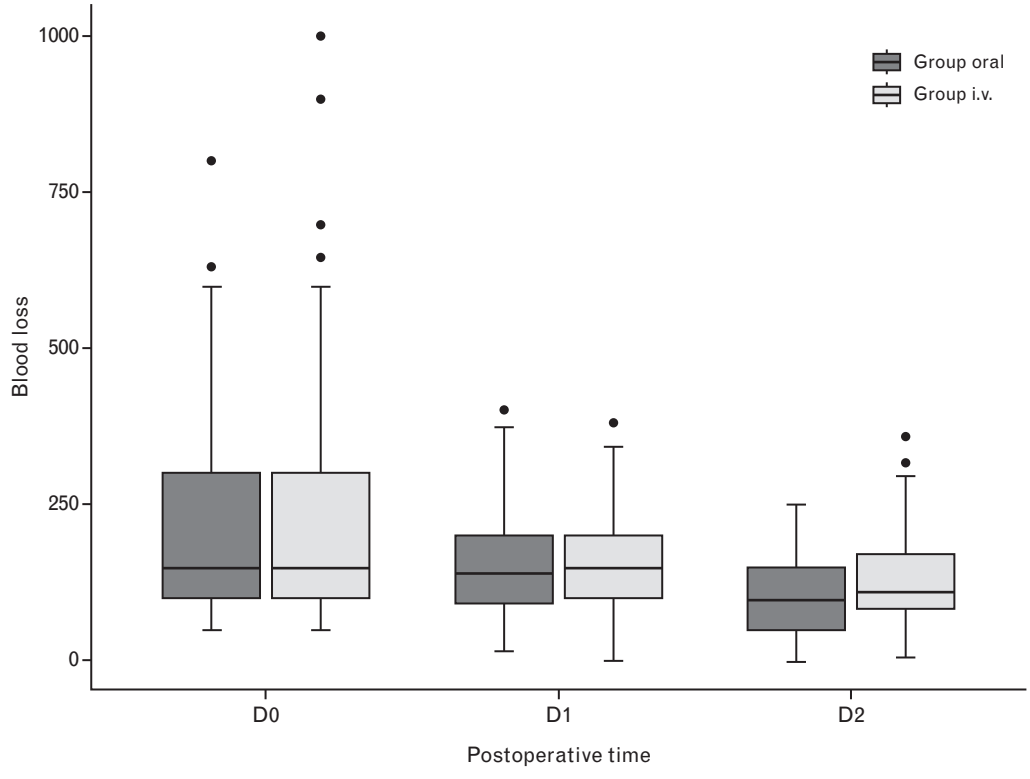
Fig. 4 Evolution of measured total blood loss over the time points of interest (D0, intra-operative blood loss; D-1, one day after surgery; D-2, 2 days after surgery) in Group oral (dark grey) and in Group i.v. (light grey).



Group oral : EMM (ml)	220.2	147.9	105.6
95% CI	186.5 to 253.9	131.2 to 164.6	91.7 to 119.4
Group i.v.: EMM (ml)	224.7	152.9	125.3
95% CI	191.7 to 257.6	136.6 to 169.2	111.7 to 138.8
Mean difference (ml)	–4.5	–5.0	–19.7
95% CI	–51.6 to 42.7	–28.3 to 18.4	–39.1 to 0.3

Note:
Estimated Marginal Means (EMM)

Numbers in the table have been rounded up to the first decimal, with the 95% confidence interval (95% CI) of the means and of the mean difference. Bold line, median; lower bound of box = lower quartile value; upper bound of box = upper quartile value; lower error bar = minimum value; upper error bar = maximum value; dots correspond to outliers.

population they excluded from their study, constituted a lack for the generalisability of their results.[23] Our study confirms their results and stands out as more inclusive and larger in the context of THA, because we applied less exclusion criteria than them. With these results confirming their conclusions, we are now in a position to state that oral TXA is an alternative to the i.v. form, in almost all patients scheduled for primary PLTHA, except for those that were excluded from our study (known allergy to TXA, renal insufficiency, recent thromboembolic disease, history of bariatric surgery, uncontrolled diabetes).

A secondary benefit of oral TXA, being as efficient as the i.v. route, is the pharmaco-economic optimisation. Although the exact cost of oral and i.v. administration is not easy to assess, depending on the supply chain or country, the financial gain is estimated to range between $33 and 94 ($14 for the oral dose as compared to $47 to 108 for the i.v. dose), or 70 to 90%, depending on the considered studies.[10,24,25] In Belgium in 2023, a 2 g oral dose of TXA costs €2.66, and a 1 g i.v. dose €4.15. With the cost of the infusion set and 0.9% saline, a price ratio of 1/4 to 1/5 between these two forms is estimated. In addition, the

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workload of nurses regarding the preparation and administration of the medication is lighter when considering the oral form. Although cost savings related to nurse workload reduction is not easy to assess with precision, one may expect additional gain here, not only in terms of money, but also in terms of benefits for the healthcare system efficiency. Since the COVID pandemic, hospitals suffer from nurse shortage. In our institution, we have moved from four nurses in a unit of 30 beds, to two or three nurses, and wards are increasingly staffed with mixes of both nurses and auxiliary nurses. Auxiliary nurses cannot prepare drugs for i.v. administration, but can give oral tablets, prepared by the nurses, to the patients. Hence, switching from the i.v. to the oral route may be an advantageous alternative in this context.

Our study has limitations. Firstly, although the moment of the oral administration of pre-operative TXA did not conform to what was defined in the study protocol initially (Fig. 3), all patients received the oral dose within a narrow time range (99% CI: -147 to -132). However, most patients received the oral dose more than 2 h prior to skin incision. Plasma TXA concentrations in the range of 10 to 15 mg l^{-1} are required to ensure maximum inhibition of fibrinolysis.[16] For oral TXA, this target concentration is reached after 66 min and remains effective for 2.7 h.[17] Despite an administration occurring earlier than scheduled, no impact on peri-operative bleeding was noted. Insofar as our trial reflects real-life clinical practice, it constitutes a supplementary argument in favour of oral administration. Indeed, the organisational constraints of an operating theatre rarely allow premedication to be administered within a rigid time frame. One may question whether administering a higher dose of oral TXA would be of any benefit, but this does not seem to be the case when looking at the results of previous studies.[5,6] Current consensus recommend the use of the lowest dose required to achieve the effective concentration (i.e. 1 g i.v. or 2 g orally).[17] In addition, administering multiple doses does not seem to offer additional blood saving as compared to a single dose, at least for relatively short surgeries such as THA.[6,18] Nevertheless, the use of TXA through any route remains more effective than placebo.[3,18] Secondly, our quantification of TBL took account of intra-operative and postoperative external losses in suction tank and drain, but neglected occult losses retained in drapes and pads. Several studies have attempted to demonstrate a reliable way of assessing these occult losses, but none of them succeeded. Consequently, in the absence of a 'gold standard', external losses are commonly used as the primary outcome.[22,26] This method, combined with a large sample size, allows reliable approximation, with occult losses impacting all patients in a similar way. To overcome this limitation, we assessed the CTBL, and came to identical conclusions. Thirdly, the incidence of complications, including venous thromboembolism, cardiac events, or length of stay was not recorded in our study. The safety of TXA has been assessed in two recent meta-analyses, which concluded that TXA administration is not associated with increased complications rates.[7,8] Furthermore, in patients receiving TXA and suffering from renal failure, the risk of seizures is low, and mainly related to TXA plasma concentrations.[27] With the doses we used, either oral or i.v., this risk remained low. Oral TXA safety profile is certainly better in this respect because the oral route creates smoothing the peak of plasma concentration.

In conclusion, the results of our monocentric clinical trial confirm the noninferiority of oral TXA to i.v. TXA with regard to blood loss in PLTHA, and thus an appealing alternative to the i.v. route as part of the second pillar of a patient blood management programme for major orthopaedic surgery.

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