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Clinical Investigation

CLINICAL INVESTIGATION

Pharmacokinetics of intramuscular tranexamic acid in bleeding trauma patients: a clinical trial

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Abstract

Background: Intravenous tranexamic acid (TXA) reduces bleeding deaths after injury and childbirth. It is most effective when given early. In many countries, pre-hospital care is provided by people who cannot give i.v. injections. We examined the pharmacokinetics of intramuscular TXA in bleeding trauma patients.

Methods: We conducted an open-label pharmacokinetic study in two UK hospitals. Thirty bleeding trauma patients received a loading dose of TXA 1 g i.v., as per guidelines. The second TXA dose was given as two 5 ml (0·5 g each) i.m. injections. We collected blood at intervals and monitored injection sites. We measured TXA concentrations using liquid chromatography coupled to mass spectrometry. We assessed the concentration time course using non-linear mixed-effect models with age, sex, ethnicity, body weight, type of injury, signs of shock, and glomerular filtration rate as possible covariates.

Results: Intramuscular TXA was well tolerated with only mild injection site reactions. A two-compartment open model with first-order absorption and elimination best described the data. For a 70-kg patient, aged 44 yr without signs of shock, the population estimates were 1.94 h^{-1} for i.m. absorption constant, 0.77 for i.m. bioavailability, 7.1 L h^{-1} for elimination clearance, 11.7 L h^{-1} for inter-compartmental clearance, 16.1 L volume of central compartment, and 9.4 L volume of the peripheral compartment. The time to reach therapeutic concentrations (5 or 10 mg L^{-1}) after a single intramuscular TXA 1 g injection are 4 or 11 min, with the time above these concentrations being 10 or 5.6 h, respectively.

Conclusions: In bleeding trauma patients, intramuscular TXA is well tolerated and rapidly absorbed.

Clinical trial registration: 2019-000898-23 (EudraCT); NCT03875937 (ClinicalTrials.gov).

Keywords: antifibrinolytic; clinical trial; haemorrhage; intramuscular; tranexamic acid; trauma

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Editor's key points

- Early administration of i.v. tranexamic acid can help prevent haemorrhage-related deaths in trauma and childbirth.
- This prospective, open-label study examined the pharmacokinetics of i.m. tranexamic acid injections in bleeding trauma patients.
- Tranexamic acid was rapidly absorbed, even when hypovolaemic shock was present, and reached therapeutic plasma concentrations within 15 min.
- Use of the i.m. route may facilitate and increase use of this potentially life-saving drug in trauma and other bleeding patients, especially in low- and middle-income countries.

Intravenous tranexamic acid (TXA) reduces bleeding deaths after injury and childbirth.[1,2] When given within an hour of bleeding onset, TXA reduces haemorrhage deaths by one-third.[3] Thereafter, the survival benefit decreases by about 10% for every 15 min treatment delay until around 3 h after which there is no benefit.[3] In high-income countries, paramedics give an i.v. injection of TXA at the scene of the injury or in the ambulance.[4] However, securing i.v. access can be difficult, particularly in trapped patients. Rapid TXA treatment is particularly challenging in low- and middle-income countries that lack formal pre-hospital care systems.[5,6] In the absence of highly trained staff, bystanders or police officers provide basic first aid.[7,8] Patients are usually taken to the nearest primary healthcare centre, often in private vehicles or rudimentary ambulances, where they receive basic care (tetanus toxoid, suturing, and X-rays) before transfer to a tertiary hospital.[9] As a result, few patients receive TXA within 3 h of injury and hardly any within the first hour.[10] If TXA could be given intramuscularly, it could be given by trained first responders, police officers, ambulance drivers, and primary care nurses with important reductions in time to treatment.

Intramuscular TXA might also increase access to treatment for women with postpartum haemorrhage (PPH). In low- and middle-income countries, about 40% of women deliver at home. Although community health workers are often present, most cannot give i.v. drugs. Transport to hospital can take hours, and many women exsanguinate on the way. Although i.v. TXA is the treatment of choice, this is not an option for tens of thousands of women. Finding alternative routes to give TXA in women with PPH is a WHO research priority.[11]

Studies in healthy volunteers show that therapeutic TXA concentrations (5–10 mg L^{-1}) are reached within 30 min after i.m. injection of TXA 500 mg.[12,13] If absorption is as rapid in trauma patients, then the i.m. route could be an alternative to i.v. use. The main uncertainty is the impact of bleeding on muscle absorption of TXA. Acute blood loss leads to compensatory cardiovascular changes that maintain blood flow to vital organs at the expense of peripheral tissues. Skin and skeletal muscle are main targets for this response with significant reductions in muscle blood flow.[14] This could reduce the absorption of TXA from muscle. To resolve this uncertainty, we examined the pharmacokinetics of i.m. TXA in bleeding trauma patients.

Methods

We conducted a prospective, open-label pharmacokinetic study in the emergency departments of two London hospitals. Adult (patient appears to be at least 16 yr old) trauma patients who had received an i.v. TXA 1 g loading dose, either pre-hospital or in-hospital, were eligible if a second TXA dose was indicated. These patients received the second TXA 1 g dose by i.m. injection at least 90 min after the first injection. The i.m. dose was given as two 5 ml (0.5 g each) injections into the thigh (*rectus femoris* or *vastus lateralis*), gluteal, or deltoid muscles, depending on the clinical situation (e.g. considering the type of injury). The dose was divided to reduce the volume injected into each muscle (5 ml is considered the upper limit). The i.m. injections were given into non-injured muscles using the Z-track method to reduce TXA leakage.[15] Trial participants had experienced a sudden life-threatening injury with significant bleeding. If appropriate, the treating doctor explained the trial procedures, and if the patient was competent, written consent was sought. If capacity was impaired and a personal or professional representative was available, then consent was sought from the representative. If neither was able to provide consent, then consent was waived and the patient was told about the trial and consent obtained for ongoing data collection as soon as possible. The Health Research Authority and London–Chelsea Research Ethics Committee (19/LO/0945) approved the trial.

We collected baseline data on age, sex, height, weight, ethnic origin (because it affects glomerular filtration rate [GFR]), time of injury and i.v. TXA administration, blood pressure, temperature, heart, ventilatory frequency, and the presence or absence of signs of shock (a clinical judgement made by the treating doctor). We collected blood test results (base excess, lactate, and creatinine) to assess shock and renal function. All physiological parameters were collected immediately before the i.m. TXA injection.

The blood sampling schedule was as follows: 10 min after i.v. injection; immediately before the i.m. injection; and 15 min, 45 min, 90 min, 3 h, 6 h, and 10 h afterwards. Because patient care had priority over sampling, we expected sampling times to vary from those shown. If we could not obtain a sample at the scheduled time, we collected blood as soon as possible and recorded the collection time. We collected 2 ml of blood in tubes without anticoagulant (BD Vacutainer® EST™ Blood Collection Tubes, Becton, Dickinson UK Limited). We took blood from a cannula to avoid multiple venepunctures. We centrifuged samples for 10 min at 1500 *g* and transferred the serum to a storage tube, which was stored at −80°C before shipment to the laboratory. Each time blood was taken, we inspected the i.m. injection sites for reactions. We continued to inspect once daily for 7 days or until prior hospital discharge. We also recorded blood pressure, temperature, heart, and ventilatory frequency. We collected data on treatments that may influence TXA concentrations (e.g. blood products and i.v. fluids) from the time of the i.m. injection to the time of the last sample. Adverse events were recorded for up to 7 days. We measured TXA concentrations using liquid chromatography coupled to mass spectrometry. The method is linear in the range 1.0–1000.0 μg ml^{-1}, accuracy is between 88.4% and 96.6%, and precision <3.0%.[16,17]

Table 1 Patient characteristics and treatments. Continuous data are presented as mean (standard deviation). Glomerular filtration rate calculated using the Modification of Diet in Renal Disease (MDRD) study group equation. TXA, tranexamic acid.

Parameter	Number of patients
Number of patients, *n*	30
Type of injury (blunt/penetrating), *n*	24/6
Male/female, *n*	26/4
Age (yr)	50 (23)
Body weight (kg)	78 (14)
Height (cm)	174 (9)
BMI (kg m^{-2})	26 (4)
Ethnicity (Asian/Black/mixed/White)	3/2/1/24
Serum creatinine (μM)	109 (28)
MDRD glomerular filtration rate (ml min^{-1} $[1.73\ m^2]^{-1}$)	72 (20)
Clinical signs of shock (yes/no), *n*	18/12
Site of injection (both i.m. doses into rectus femoris/vastus lateralis/gluteal/deltoid/different muscles)	2/8/1/17/2
Time between injury and i.v. TXA dose (h)	1.1 (0.7)
Time between i.v. and i.m. TXA doses (h)	1.8 (0.3)
Systolic blood pressure (mm Hg)	114 (27)
Blood gas lactate (mM)	4 (4)
Blood product transfusion (yes/no)	23/7
Number of red cell units transfused	3 (2)

We analysed the data using the non-linear mixed-effect modelling programme Monolix 2019R2 http://lixoft.com/products/monolix/).[18] We computed maximum likelihood estimators of the parameters without any approximation of the model (no linearisation) using the stochastic approximation expectation maximisation algorithm combined to a Markov chain Monte Carlo procedure. To ensure convergence, the iteration number was fixed at 2000. For two-compartment models, the parameters were the first-order i.m. absorption constant (k_a), i.m. bioavailability (F), elimination clearance (Cl), inter-compartmental clearance (Q), volume of the central compartment (Vc), and volume of the peripheral compartment (Vp).

The equations were as follows:

$$dA_M(t)/dt = -k_a x A_M(t)$$

$$dA_1(t)/dt = k_a \times A_M(t) - k_{10} \times A_1(t) - k_{12} \times A_1(t) + k_{21} \times A_2(t)$$

$$dA_2(t)/dt = k_{12} \times A_1(t) - k_{21} \times A_2(t)$$

where A_M is the amount of drug in the muscle for the i.m. route (0 for the i.v. route), A_1 and A_2 are the amounts of drug in the compartments, k_{10}=Cl/Vc, k_{12}=Q/Vc, and k_{21}=Q/Vp.

We investigated different error models (additive, proportional, or combined) to describe residual variabilities (ε), and the between-subject variabilities (η) were ascribed to an exponential model. We used the Bayesian information criterion to test different hypotheses about the model, specifically, covariate effects on parameters, the residual variability model, and the structure of the variance–covariance matrix for the ω parameters. We examined the effect of the following covariates: age, sex, body weight (BW), BMI, GFR, ethnicity, type of injury, presence of shock, blood lactate, and site of i.m. injection. GFR was calculated according to the Modification of Diet in Renal Disease equation.[19] Parameter estimates were standardised for a mean standard covariate using a power function: $P_i = P_{STD} \times (COV_i/COV_{STD})^{PWR}$, where P_{STD} is the standard value of the parameter, and P_i and COV_i are the parameter and covariate values of the ith individual. The PWR exponents were estimated from the data. However, for BW, powers of 1 and 0.75 for volumes and clearances, respectively, are consistent with allometric scaling theory.[20] We evaluated the goodness of fit of each model by visual inspection of individual concentration–time courses, observed–predicted (population and individual) concentration plots, and prediction-corrected visual predictive checks. Parameter confidence intervals

Table 2 Parameter estimates of the final tranexamic acid population model. Parameters normalised to 70 kg patient using allometric scaling and to a 44-yr-old patient without signs of shock. BSV, between-subject variability (η); BW, body weight; CI, confidence interval; Cl, elimination clearance; F, i.m. bioavailability; k_a, apparent constant of i.m. absorption; N/A, not applicable; Q, inter-compartmental clearance; SoS, clinical sign of shock (0 if no; 1 if yes); Vc, volume of the central compartment; Vp, volume of the peripheral compartment. *F has a logit distribution; therefore, BSV for F is the BSV of the logit.

Parameter	Covariate effect	Estimate (bootstrap 90% CI)	BSV (bootstrap 90% CI)
k_a (h^{-1})		1.94 (1.45–2.53)	0.52 (0.35–0.68)
F		0.77 (0.67–0.91)	1·05* (0.52–1.74)
Cl (L h^{-1} $[70\ kg]^{-1}$)		7.1 (5.9–8.5)	0.36 (0.23–0.44)
θ_{BW}	$(BW/70)^{\theta BW}$	0.75 (fixed)	
θ_{Age}	$(Age/44.2)^{\theta Age}$	−0.428 (−0.702 to −0.170)	
θ_{SoS}	$e^{\theta SoS \times SoS}$	−0.642 (−0.833 to −0.403)	
Q (L h^{-1} $[70\ kg]^{-1}$)		11.7 (7.0–16.3)	
θ_{BW}	$(BW/70)^{\theta BW}$	0.75 (fixed)	
Vc (L $[70\ kg]^{-1}$)		16.1 (13.8–19.1)	0.20 (0.10–0.30)
θ_{BW}	$(BW/70)^{\theta BW}$	1 (fixed)	
θ_{Age}	$(Age/44.2)^{\theta Age}$	0.746 (0.309–0.949)	
θ_{SoS}	$e^{\theta SoS \times SoS}$	−0.408 (−0.658 to −0.223)	
Vp (L $[70\ kg]^{-1}$)	$(BW/70)^{\theta BW}$	9.4 (7.8–11.5)	0.31 (0.14–0.45)
θ_{BW}		1 (fixed)	
Residual variability proportional	N/A	0.14 (0.11–0.16)	N/A

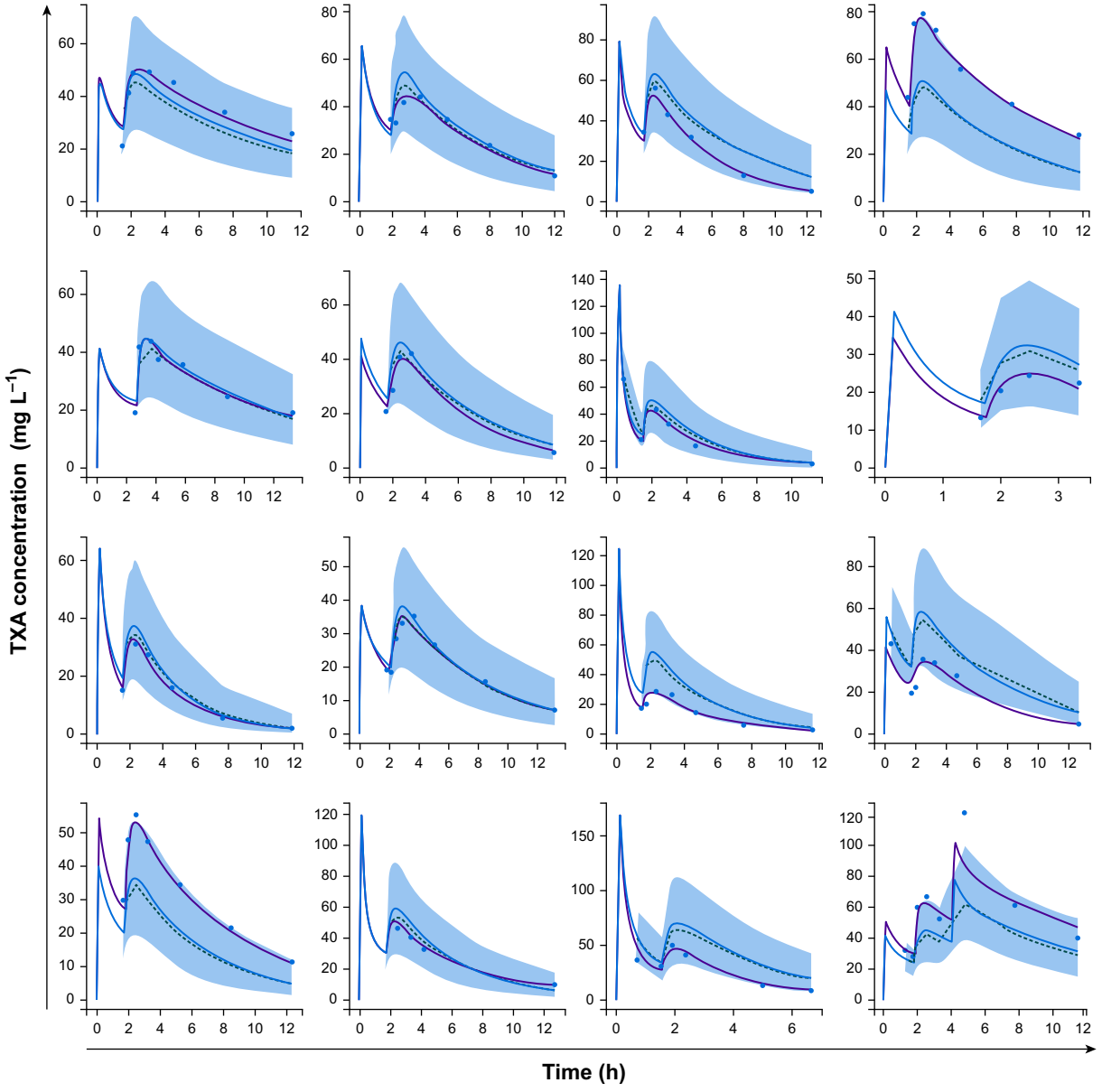

Fig 1. Tranexamic acid (TXA) concentration with time in 30 patients. Time zero is time of i.v. injection; • denotes observations, green line is population prediction, dashed line is predicted median, purple line is individual prediction, and blue shaded area is the 90% prediction interval.

were obtained using non-parametric bootstrapping with the Rsmlx R package with n=400 bootstrap replications.

Because we aimed to determine the pharmacokinetics of i.m. TXA and patients received an i.v. dose before the i.m. dose, we simulated the concentration–time profiles for a single 1 g i.m. dose and for a single 0·5 g i.m. dose. The estimated TXA concentration needed to inhibit fibrinolysis *in vitro* is in the range 5–10 mg L^{-1}.[21] We simulated the time taken to reach and the time spent above these TXA concentrations. A protocol was prepared before the analyses, which specified the statistical analyses to be conducted and is available on our data sharing website. This study was registered on EudraCT (2019-000898-23; registration date: February 5, 2019) and on ClinicalTrials.gov (NCT03875937; https://clinicaltrials.gov/ct2/show/NCT03875937; registration date: March 15, 2019).

Results

We enrolled 31 patients, but one was withdrawn before receiving i.m. TXA. Table 1 shows the characteristics of 30 patients who received i.m. TXA. There were 26 males and four females, with a mean age of 50 yr and a mean BW of 78 kg. The

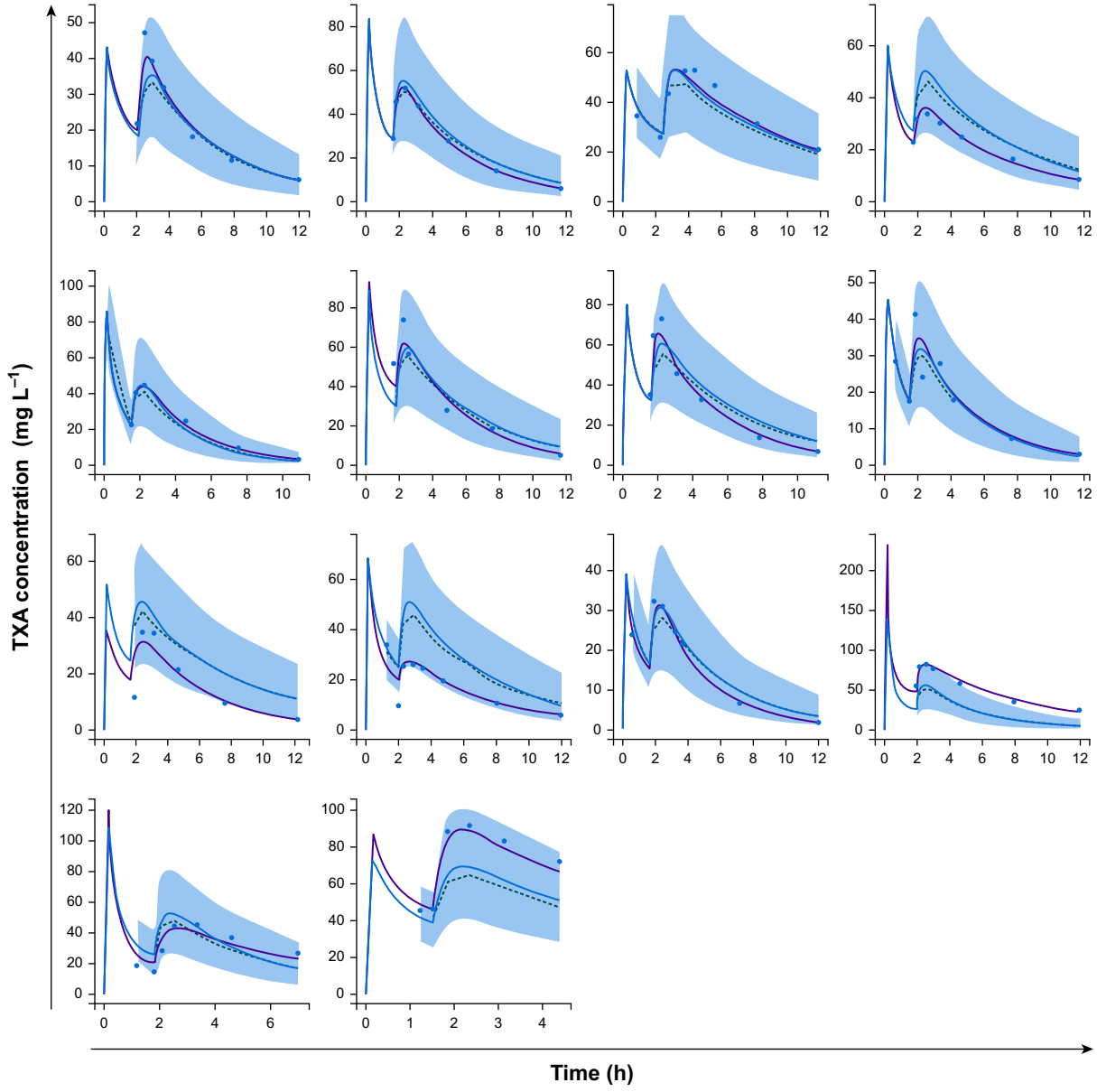

Fig 1. (*continued*)

median systolic and diastolic blood pressure were 115 mm Hg (lower quartile [LQ]=96; upper quartile [UQ]=136) and 70 mm Hg (LQ=57; UQ=78), respectively. The median base excess, serum lactate, and serum creatinine were −4 mM (LQ=−7; UQ=0), 3 mM (LQ=2; UQ=6), and 101 μM (LQ=94; UQ=127), respectively. Clinical signs of shock were seen in 18 patients, and 23 received blood products with a median of 2 units of red cells transfused (LQ=1; UQ=4). Patients with signs of shock had a lower median systolic blood pressure (97.5 mm Hg; LQ=89; UQ=120 *vs* 136 mm Hg; LQ=126; UQ=151) and a higher blood lactate (3.6 mM; LQ=2.5; UQ=5.6 *vs* 2.3 mM; LQ=1.95; UQ=3.4) than those without signs of shock. Of the 30 patients that received i.m. TXA, two had erythema, four had induration and subcutaneous nodules, and eight had bruising at the injection site. No patients had erythema, induration, or subcutaneous nodules beyond the day of injection. There was one adverse event (pyrexia 2 days after the i.m. injection) and no serious adverse events.

Pharmacokinetic modelling

We obtained 239 serum samples. A two-compartment open model with first-order absorption and elimination best described the data. The model building steps are shown in Supplementary Table 1. Adding the effect of allometrically scaled BW on Cl, Q, Vc, and Vp; age on Cl and Vc; and clinical

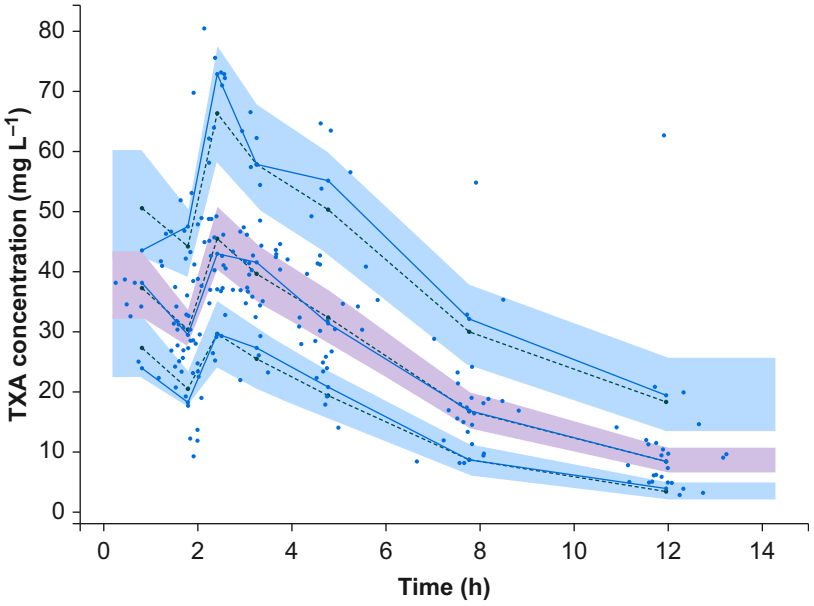

Fig 2. Diagnostic plots for the final population pharmacokinetic model: prediction-corrected visual predictive check for tranexamic acid (TXA) concentrations. Blue dots depict measured TXA concentrations. The solid centre lines and the shaded areas stand for the median of observations and the 95% confidence interval of the predictions in the time intervals.

signs of shock on Cl and Vc improved model performance. Injection site, blood lactate, and BMI had no effect on i.m. absorption parameters. In the same way, any influence of signs of shock on the absorption constant was not supported by both analysis of variance (P=0.12) and Wald tests (P=0.35), which were performed to evaluate whether this covariate should be added to the model. Similarly, for F, no covariate improved model performance. Sex, ethnicity, GFR, and type of injury had no apparent effect on the pharmacokinetics. Table 2 shows the population pharmacokinetic estimates, and Fig. 1 shows the individual TXA concentration–time profiles. For a 70 kg patient, aged 44 yr without signs of shock, the population estimates were 1.94 h^{-1} for i.m. absorption constant (i.e. a 21.4 min absorption half-life), 0.77 for i.m. bioavailability, 7.1 L h^{-1} for elimination clearance, 11.7 L h^{-1} for inter-compartmental clearance, 16.1 L for the volume of the central compartment, and 9.4 L for the volume of the peripheral compartment. For the same patient with signs of shock, the estimates were 3.7 L h^{-1} for elimination clearance and 10.7 L for volume of the central compartment.

Between-subject variabilities were estimated for k_a, F, Cl, Vc, and Vp using an exponential model, and the residual variability was estimated using a proportional error model. Figure 2 shows the prediction-corrected visual predictive check plot for the final population pharmacokinetic model with further diagnostic plots (predicted *vs* observed concentrations; residuals and normalised prediction distribution error plots and convergence diagnosis) shown in Supplementary Figs 1–3.

Simulations

Figure 3 shows simulated concentration–time profiles after a single TXA dose 1 g i.m. After a single TXA dose 1 g i.m., a TXA concentration of 5 mg L^{-1} would be achieved in about 4 min, remaining above this level for 10 h. A TXA concentration of 10 mg L^{-1} would be achieved in about 11 min, remaining above this level for 5.6 h. After a TXA dose 0.5 g i.m., a TXA concentration of 5 mg L^{-1} would be achieved in about 10 min, remaining above this level for 5.8 h. A TXA concentration of 10 mg L^{-1} would be achieved in 22 out of 30 patients in about 20 min, remaining above this level for 2.8 h.

Discussion

Intramuscular TXA is well tolerated with only mild and transient injection site reactions. Intramuscular TXA is rapidly absorbed, reaching therapeutic concentrations within 15 min. Blood lactate and signs of shock had no apparent impact on the rate of absorption. Our results have major implications for trauma care, particularly in low- and middle-income countries where i.m. TXA could expand access to treatment.

Strengths and weaknesses

Our study is the first to examine serum concentrations and pharmacokinetics of i.m. TXA in bleeding trauma patients. We obtained data from 30 patients with eight data points per patient and sampling for up to 12 h. Because TXA is life-saving and treatment delay reduces the survival benefit, all

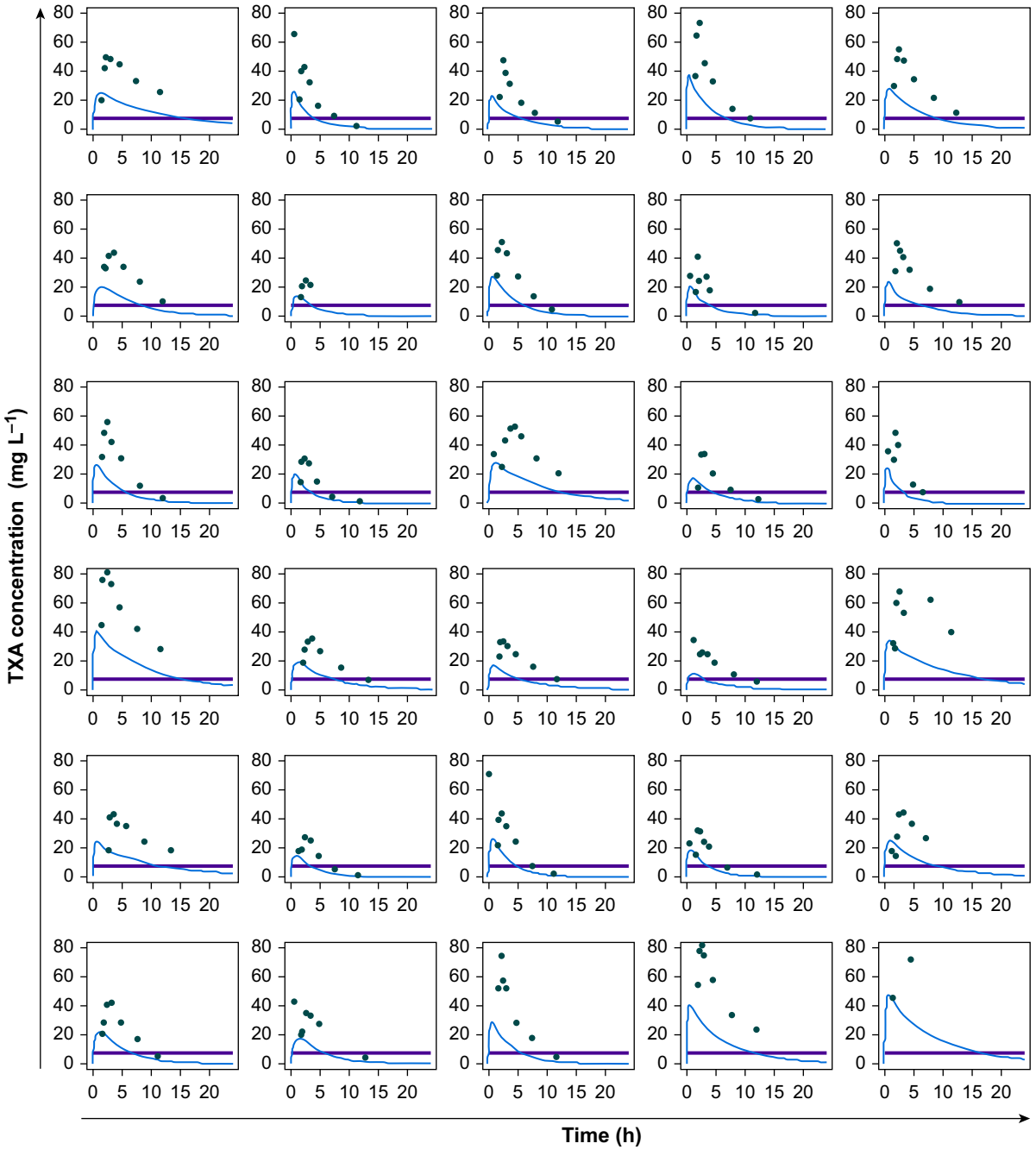

Fig 3. Simulated individual concentration–time profiles of tranexamic acid (TXA) in 30 patients had they only received a 1 g i.m. dose. Grey dots (•) show the real observations after a 1 g i.v. dose, and then a 1 g i.m. dose. The green area shows the concentration range 5 and 10 mg L^{-1}. Signs of shock were taken into account as observed individually for each patient.

participants received the initial 1 g loading dose intravenously. However, because the 1 g maintenance infusion is often interrupted for diagnostic tests (e.g. CT scanning) or surgery and is sometimes omitted completely, we had no reason to believe that giving the maintenance dose intramuscularly would put patients at risk. At the same time, we believe that the study population is representative of bleeding trauma patients. More than half of the patients had signs of shock, and the median blood lactate was 3.6 mM.

Prior administration of an i.v. dose allowed calculation of the absolute bioavailability by the i.m. route, although TXA losses to haemorrhage may have resulted in some time-dependant changes in pharmacokinetic parameters and underestimation of bioavailability.[22] Although we attempted to

obtain a blood sample 10 min after the i.v. injection, because patient care was the priority, in many cases this was not possible. However, we were able to collect samples before the i.m. dose. With the samples obtained, we built a pharmacokinetic model that provided the necessary pharmacokinetic parameters. The parameter estimates we obtained are consistent with those from healthy volunteers and with population models of i.v. TXA in trauma patients.[23,24] Although the effect of age was not detected in previous studies, most were in different patient populations. The only previous report in this patient population had a single sampling point per patient, which makes covariate identification and parameter estimation difficult.[23] Importantly, simulations for patients between 25 and 80 yr old without signs of shock and receiving a single i.m. 1 g dose show that concentrations above the desired threshold are maintained for several hours in all patients, regardless of age (Supplementary Fig. 4).

The target therapeutic concentrations (5–10 mg L^{-1}) were obtained from a systematic review of *in vitro* pharmacodynamic studies. In most of the included studies, high concentrations of fibrinolytic activators were added to blood to speed up fibrinolysis. Because the concentrations used were higher than those seen in even the most severely injured patients, results from *in vitro* studies may have overestimated the concentration of TXA needed to inhibit fibrinolysis *in vivo*. Although a combined pharmacokinetic–pharmacodynamic study may have been preferable, collection of data on fibrinolytic markers was not possible in this emergency situation.

Implications

Every year, around five million people worldwide die from injuries.[25] There are one-and-a-half times more injury deaths than deaths from human immunodeficiency virus, tuberculosis, and malaria combined. More than 90% of trauma deaths are in low- and middle-income countries, with up to 80% of deaths occurring before hospital arrival.[26] Tranexamic acid safely reduces mortality in bleeding trauma patients. Tranexamic acid is heat stable, inexpensive, and has a long shelf life. Treatment is highly cost effective in high-, middle-, and low-income countries.[27] However, urgent treatment is essential. The evidence that i.m. TXA is well tolerated and rapidly absorbed, even in patients with clinical signs of shock, raises the possibility that i.m. TXA could be given by trained first responders, police officers, ambulance drivers, and primary care nurses, thus greatly expanding timely access to treatment for patients in low- and middle-income countries. Because shock had no apparent effect on TXA absorption but reduced elimination, therapeutic concentrations are achieved slightly sooner in the most severely injured patients who have the most to gain from TXA treatment. Prompt treatment would be facilitated by development of a low-cost, easy-to-use auto-injector or pre-filled syringes for use by first-aiders. An easy-to-use TXA auto-injector would also allow wounded soldiers to administer i.m. TXA to themselves or their colleagues as soon as possible after wounding to maximise survival.[28]

The lack of any adverse reactions and rapid absorption suggest that i.m. TXA might also have the potential to increase timely access to treatment for women with PPH. However, because physiological changes during pregnancy could affect the distribution and renal elimination of TXA, our results cannot be generalised to women with PPH, and pharmacokinetic studies in pregnant women are underway (https://clinicaltrials.gov/ct2/show/NCT04274335).

Data sharing

After publication of the primary and secondary analyses, individual de-identified patient data from the trial will be made available via our data sharing portal The Free Bank of Injury and Emergency Research Data website (http://freebird.Lshtm.ac.uk) indefinitely. The trial protocol, statistical analysis plan, and trial publication will be also available at this site.

Authors' contributions

Study design: HS-S, RP, IR
Drafting of protocol: HS-S, RP, HJ, PM, JP, NT, HP, IR
Conducting of pharmacokinetic methodology: SG-D
Management of trial: LF
Trial administration: CG
Study supervision: HS-S, IR
Performing of assays: EL
Modelling: SU
Data management: DP
Data handling: AT
Data analysis: SG-D
HJ was the principal investigator at St George's Hospital, RD was the principal investigator at The Royal London Hospital, WM was deputy principal investigator at St George's Hospital, PM was at St George's Hospital and JP was the investigator at The Royal London Hospital. All authors were responsible for reviewing and revising the paper, and have approved the final version. The corresponding author had full access to all the data and had final responsibility for the decision to submit for publication.

Declarations of interest

The authors declare that they have no competing interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2020.07.058.

References

1. CRASH-2 trial collaborators. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2):

a randomised, placebo-controlled trial. *Lancet* 2010; **376**: 23–32
2. WOMAN trial collaborators. Effect of early tranexamic acid administration on mortality, hysterectomy, and other morbidities in women with post-partum haemorrhage (WOMAN): an international, randomised, double-blind, placebo-controlled trial. *Lancet* 2017; **389**: 2105–16
3. Gayet-Ageron A, Prieto-Merino D, Ker K, Shakur H, Ageron F, Roberts I, Antifibrinolytic Trials Collaboration. Effect of treatment delay on the effectiveness and safety of antifibrinolytics in acute severe haemorrhage: a meta-analysis of individual patient-level data from 40 138 bleeding patients. *Lancet* 2017; **391**: 125–32
4. Marsden M, Rossetto A, Duffield C, et al. Prehospital tranexamic acid shortens the interval to administration by half in Major Trauma Networks: a service evaluation. *Emerg Med J* 2019; **36**: 395–400
5. Mould-Millman N, Dixon J, Sefa N, et al. The state of Emergency Medical Services (EMS) systems in Africa. *Prehosp Disaster Med* 2017; **32**: 273–83
6. Kironji A, Hodkinson P, de Ramirez S, et al. Identifying barriers for out of hospital emergency care in low and low-middle income countries: a systematic review. *BMC Health Serv Res* 2018; **18**: 291
7. Bhalla K, Sriram V, Arora R, et al. The care and transport of trauma victims by layperson emergency medical systems: a qualitative study in Delhi, India. *BMJ Glob Health* 2019; **4**, e001963
8. Wesson H, Stevens K, Bachani A, et al. Trauma systems in Kenya: a qualitative analysis at the district level. *Qual Health Res* 2015; **25**: 589–99
9. Radjou AN, Mahajan P, Baliga DK. Where do I go? A trauma victim's plea in an informal trauma system. *J Emerg Trauma Shock* 2013; **6**: 164–70
10. Thurston B, Chowdhury S, Edu S, Nicol A, Navsaria P. Time since injury is the major factor in preventing tranexamic acid use in the trauma setting: an observational cohort study from a major trauma centre in a middle-income country. *S Afr J Surg* 2015; **53**: 13–8
11. World Health Organization. *Updated WHO recommendation on tranexamic acid for the treatment of postpartum haemorrhage* 2017. Available from: https://www.who.int/reproductivehealth/publications/tranexamic-acid-pph-treatment/en/. [Accessed 29 May 2020]
12. Puigdellivol E, Carral M, Moreno J, Pla-Delfina J, Jane F. Pharmacokinetics and absolute bioavailability of intramuscular tranexamic acid in man. *Int J Clin Pharmacol Ther Toxicol* 1985; **23**: 298–301
13. Sano M, Hakusui H, Kojima C, Akimoto T. Absorption and excretion of tranexamic acid following intravenous, intramuscular and oral administrations in healthy volunteers. *Jpn J Clin Pharmacol Ther* 1976; **7**: 375–82
14. Haljamae H. Microcirculation and hemorrhagic shock. *Am J Emerg Med* 1984; **2**: 100–7
15. Yilmaz D, Khorshid L, Dedeoğlu Y. The effect of the Z-track technique on pain and drug leakage in intramuscular injections. *Clin Nurse Spec* 2016; **30**: E7–12
16. Grassin Delyle S, Abe E, Batisse A, et al. A validated assay for the quantitative analysis of tranexamic acid in human serum by liquid chromatography coupled with electrospray ionization mass spectrometry. *Clin Chim Acta* 2010; **411**: 438–43
17. Fabresse N, Fall F, Etting I, Devillier P, Alvarez JC, Grassin-Delyle S. LC-MS/MS determination of tranexamic acid in human plasma after phospholipid clean-up. *J Pharm Biomed Anal* 2017; **141**: 149–56
18. Kuhn E, Lavielle M. Maximum likelihood estimation in nonlinear mixed effects models. *Comput Stat Data Anal* 2005; **49**: 1020–38
19. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med* 1999; **130**: 461–70
20. Anderson BJ, Holford NH. Mechanism-based concepts of size and maturity in pharmacokinetics. *Annu Rev Pharmacol Toxicol* 2008; **48**: 303–32
21. Picetti R, Shakur-Still H, Medcalf RL, Standing JF, Roberts I. What concentration of tranexamic acid is needed to inhibit fibrinolysis? A systematic review of pharmacodynamics studies. *Blood Coagul Fibrinolysis* 2019; **30**: 1–10
22. Derickson M, McClellan J, Marko S, et al. The effects of hemorrhage on the pharmacokinetics of tranexamic acid in a swine model. *J Trauma Acute Care Surg* 2018; **85**: S44–8
23. Grassin-Delyle S, Theusinger O, Albrecht R, et al. Optimisation of the dosage of tranexamic acid in trauma patients with population pharmacokinetic analysis. *Anaesthesia* 2018; **73**: 719–29
24. Grassin-Delyle S, Semeraro M, Foissac F, et al. Tranexamic acid through intravenous, intramuscular and oral routes: an individual participant data meta-analysis of pharmacokinetic studies in healthy volunteers. *Fundam Clin Pharmacol* 2019; **33**: 670–8
25. World Health Organization. *Injuries and violence: the facts* 2014. Available from: https://www.who.int/violence_injury_prevention/key_facts/en/. [Accessed 29 May 2020]
26. Reynolds T, Stewart B, Drewett I, et al. The impact of trauma care systems in low- and middle-income countries. *Annu Rev Public Health* 2017; **38**: 507–32
27. Guerriero C, Cairns J, Perel P, Shakur H, Roberts I. Cost-effectiveness analysis of administering tranexamic acid to bleeding trauma patients using evidence from the CRASH-2 trial. *PLoS One* 2011; **6**, e18987
28. Wright C. Battlefield administration of tranexamic acid by combat troops: a feasibility analysis. *J R Army Med Corps* 2014; **160**: 271–2

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