Original article

Effectiveness of early administration of tranexamic acid in patients with severe trauma

A. Shiraishi[1,3], S. Kushimoto[6], Y. Otomo[3], H. Matsui[2,4], A. Hagiwara[5] and K. Murata[3], on behalf of the Japanese Observational Study for Coagulation and Thrombolysis in Early Trauma (J-OCTET) investigators

[1]Emergency and Trauma Center and [2]Clinical Research Support Office, Kameda Medical Center, Kamogawa, [3]Trauma and Acute Critical Care Center, Tokyo Medical and Dental University Hospital of Medicine, [4]Department of Clinical Epidemiology and Health Economics, School of Public Health, University of Tokyo, and [5]Department of Emergency Medicine and Critical Care, National Center for Global Health and Medicine, Tokyo, and [6]Division of Emergency and Critical Care Medicine, Tohoku University Graduate School of Medicine, Sendai, Japan

Correspondence to: Dr A. Shiraishi, Emergency and Trauma Center, Kameda Medical Center, 929 Higashicho, Kamogawa, Chiba 296-8602, Japan (e-mail: siris.accm@tmd.ac.jp)

Background: **A reduction in mortality with the early use of tranexamic acid has been demonstrated in severely injured patients who are bleeding. However, the modest treatment effect with no reduction in blood transfusion has raised concerns. The aim of the present study was to estimate the effectiveness of regular use of tranexamic acid in severely injured patients.**

Methods: **This multicentre observational study used retrospectively collected data from consecutive injured patients (Injury Severity Score at least 16) treated in 15 Japanese academic institutions in 2012. A propensity score-matched analysis compared patients who did or did not receive tranexamic acid administration within 3 h of injury. Study outcomes included 28-day all-cause and cause-specific mortality, and need for blood transfusion.**

Results: **Of 796 eligible subjects, 281 were treated with tranexamic acid. Propensity score matching selected a total of 500 matched subjects (250 in each group). Tranexamic acid administration was associated with lower 28-day mortality (10·0 *versus* 18·4 per cent; difference −8·4 (95 per cent c.i. −14·5 to −2·3) per cent) and lower 28-day mortality from primary brain injury (6·0 *versus* 13·2 per cent; difference −7·2 (−12·3 to −2·1) per cent). However, there was no significant difference between groups in the need for blood transfusion (33·2 *versus* 34·8 per cent; difference −1·6 (−9·9 to 6·7) per cent).**

Conclusion: **Early tranexamic acid use was associated with reduced mortality in severely injured patients, in particular those with a primary brain injury.**

Paper accepted 9 January 2017

Published online 23 February 2017 in Wiley Online Library (www.bjs.co.uk). **DOI:** 10.1002/bjs.10497

Introduction

Administration of a lysine derivative such as tranexamic acid reduces the required amounts of perioperative blood transfusion in elective surgery, including cardiac, orthopaedic and vascular procedures[1,2]. In trauma care, the CRASH-2 (Clinical Randomization of an Antifibrinolytic in Significant Haemorrhage-2) trial demonstrated that intravenous administration of tranexamic acid within 3 h of the time of injury was associated with a 2·2 per cent absolute reduction in 28-day mortality in adult injured patients with significant haemorrhage or who were considered to be at risk of significant haemorrhage[3,4]. However, several researchers have questioned the interpretation of the results from this trial[5,6]. The design of the CRASH-2 trial allowed exclusion of a subject when the physician found an indication or contraindication to tranexamic acid administration in an individual injured patient[3–6]. Trauma severity was not represented using the Injury Severity Score (ISS) or blood test data for coagulation and fibrinolysis[3–6]. Regarding the CRASH-2 trial results, the use of tranexamic acid did not reduce the amount of blood transfusion required, but did significantly decrease mortality[3,4,6]. The most frequent cause of death was traumatic brain injury rather than bleeding[3,4,6]. Subsequent observational studies[7–9] have failed to reproduce the effects of tranexamic acid, presumably because of insufficient background adjustments and lack of statistical power. One exception to this is the MATTERs (Military Application of Tranexamic

Acid in Trauma Emergency Resuscitation) study, which also demonstrated a survival effect[10].

The aims of the present study were to compare 28-day mortality and blood transfusion amounts among severely injured subjects who did or did not receive tranexamic acid within 3 h of injury, based on propensity score matching that balanced for background characteristics including ISS and indicators of coagulopathy and fibrinolysis[11].

Methods

Reporting of this article adhered to the STROBE guidelines[12].

Study design and data source

J-OCTET (Japanese Observational Study for Coagulation and Thrombolysis in Early Trauma) was a multicentre observational study that investigated the associations between mortality as well as blood transfusion requirements and baseline characteristics and blood data in injured patients. This study was planned by the Committee for Future Planning of the Japanese Association for the Surgery of Trauma (JAST), and 15 JAST-certified educational hospitals for trauma care professionals participated. The ethics committee of Tohoku University Graduate School of Medicine (receipt number 2013-1-41) and the institutional review board of each participating institute approved J-OCTET. All data used in the present study were collected retrospectively from the medical record and registered in the J-OCTET database by the emergency physicians of participating hospitals in 2012. This study was designed as a retrospective analysis of data from J-OCTET to test the efficacy of early tranexamic acid administration in patients with severe trauma.

Patient selection

Injured patients aged at least 18 years with an ISS of 16 or more who were admitted to one of the study hospitals were eligible for J-OCTET. Patients were excluded if they had complications such as out-of-hospital cardiac arrest, burns, liver cirrhosis or isolated cervical spine injury not caused by a high-energy accident, or if they were pregnant. The present study included all subjects registered in J-OCTET.

Study intervention

The intervention involved intravenous administration of tranexamic acid within 3 h after injury, which was identical to a secondary analysis of the CRASH-2 trial[5,6].

Study outcomes

The primary study outcome was 28-day mortality from any cause. Secondary study outcomes included cause-specific 28-day mortality, which was classified as death from a primary brain injury, haemorrhage or other cause; the total transfusion amount of packed red blood cells (PRBCs) and fresh frozen plasma (FFP) within 24 h of the hospital visit; and any kind of thromboembolic complication during the hospital admission. To avoid the survivor bias related to there being potentially less blood transfusion for non-survivors within the 24-h period, blood transfusion amounts were estimated both for all subjects and for 24-h survivors. Blood transfusion amounts are reported in units; a unit in Japan is defined as the amount of blood product from 200 ml whole blood.

Statistical analysis

All statistical analyses were performed in R 3.2.3 for statistical computing (https://www.r-project.org/), with the add-on packages 'MASS' for robust regression and outlier removal[13], 'car' for Box–Cox transformation[14], 'mice' for multiple imputation[15], 'Matching' for propensity score matching[16], 'rms' for survival analysis[17], 'AER' for instrumental variable analysis[18] and 'miceadds' for F-statistics computation across multiply imputed data sets[19]. In all statistical analyses, statistical significance in the two-sided test was accepted at $P < 0{\cdot}050$.

Study variables and data preparation

In J-OCTET, researchers (emergency physicians) at each study hospital selected the eligible subjects and collected the study variables retrospectively (*Table S1*, supporting information). The study variables in the J-OCTET data sets were prepared in two stages before statistical analyses. In the first stage, outliers were removed from several of the continuous variables. The second stage involved multiple imputation. Strong linear correlations were observed between prothrombin time and prothrombin time international normalized ratio (INR), and between fibrin and fibrinogen degeneration products and D-dimer. However, these pairs had several outliers that could affect the regression analyses. Therefore, two-sample robust linear regression was used to detect and remove the outliers from these continuous variables (*Figs S1* and *S2*, supporting information)[13]. Because a significant number of missing values were observed for INR (11·3 per cent) and D-dimer (25·0 per cent) (*Table S1*), and these could be considered as missing at random[20], a multiple imputation by chained equations complemented all of the missing values in the study variables and generated 500 data sets with ten

iterations[15,21]. Box–Cox transformation was used to transform skewed distributions of continuous variables into normal distributions before the multiple imputation, and back to the original distribution after the multiple imputation[14]. Categorical and continuous variables are reported as counts and percentages, and as median (i.q.r.) respectively, after pooling of all the imputed data sets into a single data set. Predictive statistics determined the estimators as point estimates, and 95 per cent confidence intervals were computed and integrated across the imputed data sets using bootstrapping for the blood transfusion amounts[22] or Rubin's rule for all other analyses[21].

Propensity score matching

Logistic regression analysis was employed to compute the propensity score for the use of the study intervention in each subject from the known pretreatment variables that were considered to be associated clinically with the primary outcome of the study (*Appendix S1*, *Figs S3* and *S4*, supporting information). Propensity score matching selected subjects pairwise with or without intravenous administration of tranexamic acid on a 1 : 1 basis after all of the propensity scores across the imputed data sets had been averaged and logit-transformed (*Fig. S5*, supporting information). To achieve an appropriate match balance, absolute standardized mean differences of all variables included in the propensity score estimation were used to assess the match balance; this was considered appropriate if none of the absolute standardized mean differences exceeded 0·1 (*Figs S6* and *S7*, supporting information), and the allowable callipers used for the matching were 0·5 (upper limit) for the logit-transformed propensity score[23].

Intergroup comparisons

After the 1 : 1 propensity score matching, the primary outcome was assessed as the frequency in each group, as the absolute difference between the groups, and by using odds ratios. As regards the secondary outcomes, cause-specific 28-day mortality was assessed in a manner similar to that for the primary outcome. In addition, 24-h blood transfusion amounts were assessed as the units of blood products and absolute differences between groups. Bootstrap estimation was repeated 200 times for each imputed data set, and a total of 100 000 times over 500 imputed data sets to estimate the average and intergroup differences, with 95 per cent confidence intervals for the 24-h blood transfusion amounts.

Sensitivity analysis

To test the robustness of the multiple imputation, intergroup differences in the primary outcome were assessed for the propensity score-matched subjects from the naive data set (complete-case analysis) and for those in the multiply imputed data sets (*Fig. S8*, supporting information). Instrumental variable analysis, or two-stage least squares regression analysis, can adjust not only for measured confounders but also for unmeasured confounders in regression analyses if an appropriate instrumental variable is applicable[24]. The instrumental variable is defined as a variable that is strongly associated with the probability of the study intervention, but is not associated with the study outcome[25]. It was found that years from the founding of each hospital to the study year was applicable as the instrumental variable. Linear regression analysis and two-stage least squares regression analysis was used to assess the intergroup differences in the primary outcome in the propensity score-matched cohort (*Fig. S8*, supporting information).

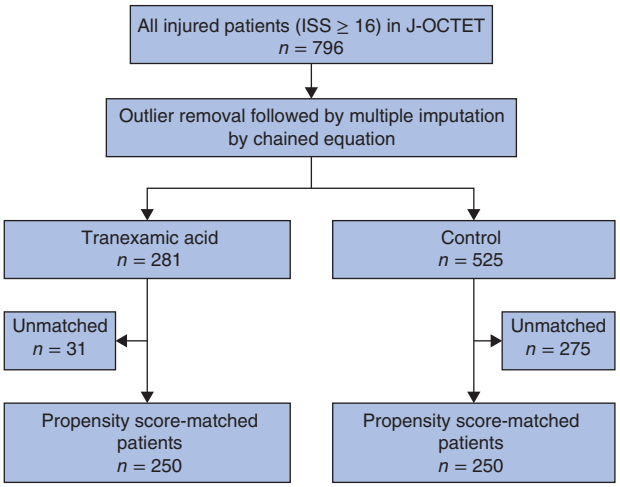


Fig. 1 Selection of participants for the study. ISS, Injury Severity Score

Results

Of the 796 subjects registered, 281 received tranexamic acid intravenously within 3 h of the injury (*Fig. 1*). No patient was reported to have received tranexamic acid more than 3 h after injury. Propensity score matching selected 250 subjects who received tranexamic acid and 250 who did not (control group). None of the absolute standardized mean differences in the variables included in the propensity score estimation exceeded 0·1 (*Table 1*); hence, the propensity score matching achieved an acceptable match balance[23].

Primary outcome

The 28-day mortality rate was 10·0 per cent with tranexamic acid administration and 18·4 per cent without; the

Table 1 Pretreatment variables of injured patients who received tranexamic acid and controls included in propensity score estimation before and after matching

	Before matching			After matching		
	Tranexamic acid ($n = 281$)	Control ($n = 515$)	SMD	Tranexamic acid ($n = 250$)	Control ($n = 250$)	SMD
Age (years)*	57 (33–72)	60 (40–72)	−0·109	57 (36–72)	56 (38–69)	−0·038
Male sex*	198 (70·5)	391 (75·9)	−0·123	181 (72·4)	186 (74·4)	−0·065
Preinjury antithrombotic use*	27 (9·6)	34 (6·6)	0·110	25 (10·0)	23 (9·2)	0·056
Blunt injury*	276 (98·2)	514 (99·8)	−0·161	249 (99·6)	249 (99·6)	0·000
Vital signs at presentation						
Respiratory rate (per min)	20 (18–25)	20 (18–25)	−0·007	20 (18–24)	20 (18–25)	−0·040
Heart rate (beats per min)	88 (76–105)	84 (72–98)	0·252	87 (75–100)	86 (75–100)	−0·015
Systolic BP (mmHg)	134 (109–157)	132 (109–156)	−0·008	136 (110–159)	133 (110–157)	0·031
Body temperature (°C)	36·2 (35·6–36·7)	36·3 (35·8–36·8)	−0·043	36·2 (35·6–36·7)	36·4 (35·9–36·8)	−0·077
Glasgow Coma Scale score	13 (7–14)	14 (10–15)	−0·229	13 (8–15)	13 (8–15)	−0·004
Traumatic brain injury*	206 (73·3)	275 (53·4)	0·422	188 (75·2)	190 (76·0)	−0·019
Injury Severity Score	25 (17–30)	22 (17–26)	0·284	25 (17–29)	25 (17–29)	−0·007
Laboratory data at presentation						
WBC count (10^3/mm^3)	11·4 (8·1–15·5)	10·5 (7·6–14·4)	0·097	10·9 (8·1–15·4)	10·5 (7·7–14·6)	0·000
Haemoglobin (g/dl)	13·1 (11·4–14·4)	13·2 (11·6–14·5)	−0·044	13·2 (11·9–14·4)	13·4 (11·7–14·6)	0·021
Platelet count (10^4/mm^3)	19·9 (15·8–24·7)	20·1 (16·3–25·0)	−0·089	20·0 (15·9–24·9)	19·4 (16·0–24·9)	0·001
INR	1·06 (0·98–1·17)	1·03 (0·98–1·11)	0·142	1·05 (0·98–1·12)	1·03 (0·98–1·12)	−0·025
Fibrinogen (mg/dl)	221 (175–273)	244 (195–291)	−0·289	225 (179–276)	235 (186–277)	−0·049
D-dimer (μg/ml)	26·3 (8·6–60·0)	20·6 (6·9–48·1)	0·099	24·2 (8·5–59·9)	25·8 (7·6–58·6)	0·000
Lactate (mmol/l)	2·8 (1·7–4·3)	2·3 (1·4–3·3)	0·249	2·6 (1·7–4·0)	2·6 (1·6–3·9)	−0·007

Values are median (i.q.r.) unless indicated otherwise; *values in parentheses are percentages. SMD, standardized mean difference; WBC, white blood cell; INR, international normalized ratio.

Table 2 Comparisons of primary and secondary outcomes in injured patients who received tranexamic acid and controls

	Tranexamic acid ($n = 250$)	Control ($n = 250$)	Absolute difference	Odds ratio
Primary outcome				
28-day mortality (%)	10·0	18·4	−8·4 (−14·5, −2·3)	0·49 (0·29, 0·83)
Secondary outcomes				
Cause-specific mortality (%)				
Primary brain injury	6·0	13·2	−7·2 (−12·3, −2·1)	0·42 (0·22, 0·88)
Haemorrhage	2·8	4·0	−1·2 (−4·4, 2·0)	0·69 (0·26, 1·85)
Any other cause	1·2	1·2	0·0 (−1·9, 1·9)	1·00 (0·20, 5·02)
Receipt of any blood transfusion (%)	33·2	34·8	−1·6 (−9·9, 6·7)	0·93 (0·64, 1·35)
Mean amount of PRBC transfused within 24 h (units*)				
Overall population	4·5	4·0	0·4 (−1·3, 2·1)	
24-h survivors	4·1	3·2	0·9 (−0·8, 2·6)	
Mean amount of FFP transfused within 24 h (units*)				
Overall population	4·7	4·0	0·7 (−1·2, 2·6)	
24-h survivors	4·3	3·3	1·0 (−1·0, 2·9)	
Thromboembolic complications (%)	1·2	2·0	−0·8 (−3·0, 1·4)	0·60 (0·14, 2·53)

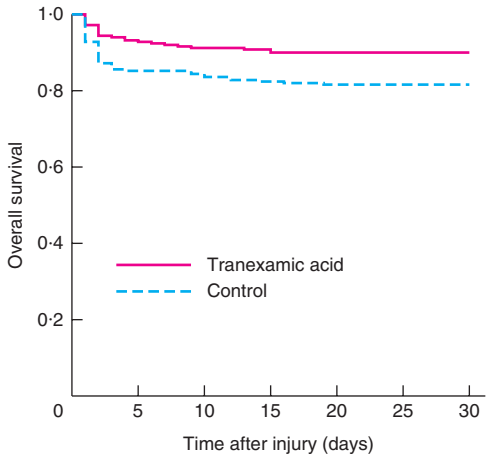
Absolute differences are reported as mean (95 per cent c.i.) based on linear regression analyses of mortality and thromboembolic complications, and on bootstrap estimation in analyses of blood transfusion amounts. Associations between tranexamic acid administration and binomial outcome variables are reported as odds ratio (95 per cent c.i.) based on logistic regression analysis. *A unit of blood transfusion in Japan is defined as blood products from 200 ml blood. PRBC, packed red blood cell; FFP, fresh frozen plasma.

absolute reduction in mortality (mean difference −8·4 (95 per cent c.i. −14·5 to −2·3) per cent was statistically significant (*Table 2*). Tranexamic acid administration was associated with extended survival (*Fig. 2*).

Secondary outcomes

In all propensity score-matched subjects, tranexamic acid administration was associated with a lower 28-day mortality rate from a primary brain injury (6·0 *versus* 13·2 per cent; mean difference (−7·2 (95 per cent c.i. −12·3 to −2·1) per cent), but not from haemorrhage or any other cause (*Table 2*).

PRBCs or FFP were administered to 83 patients (33·2 per cent) who received tranexamic acid and to 87 (34·8 per cent) who did not. There were no significant differences between the groups in the mean amount of



No. at risk

Tranexamic acid	250	233	228	227	225	225	225
Control	250	213	209	206	204	204	204

Fig. 2 Comparison of 28-day survival after injury in propensity score-matched injured patients who did or did not receive tranexamic acid. $P = 0{\cdot}007$ (log rank test)

PRBC transfused (4·5 *versus* 4·0 units; bootstrapped mean difference 0·4 (95 per cent c.i. −1·3 to 2·1) units) or FFP transfusion (4·7 *versus* 4·0 units; bootstrapped mean difference 0·7 (−1·2 to 2·6) units). Similarly, amounts of PRBC plus FFP did not differ between the groups in either the overall population or 24-h survivors (*Table 2*).

Discussion

In this study, tranexamic acid administration within 3 h after an injury reduced 28-day mortality in severely injured patients. This came largely from a reduction in 28-day mortality caused by primary brain injury. This could indicate achievement of early haemostasis for intracranial bleeding. In contrast, tranexamic acid did not contribute to reduced mortality from bleeding or blood transfusion amounts required.

Clinical evidence of the effect of early tranexamic acid administration on trauma mortality was first demonstrated in the CRASH-2 RCT[3,4]. A subsequent observational study (MATTERs)[10] demonstrated that tranexamic acid administration was associated with lower mortality in patients injured on the battlefield. Similarly, the present study demonstrated an association between reduced 28-day mortality and tranexamic acid administration (−8·4 per cent absolute reduction) in a civilian trauma population; this was similar to the 6·5 per cent reduction reported in the MATTERs study[10] and larger than the 2·2 per cent reduction in the CRASH-2 trial[3,4]. Other observational studies[8,9] demonstrated a similar overall risk of death both in patients who received tranexamic acid and in controls. In another report[7], tranexamic acid administration was associated with 8 per cent excess mortality in propensity score-matched subjects who required emergency blood transfusion and/or surgery. Such inconsistencies might be the result of different patient selection criteria. The CRASH-2 trial included injured patients with suspected ongoing haemorrhage; 50 per cent of the subjects received a blood transfusion[3,4]. In comparison, only one-third of the subjects in the present study received any kind of blood transfusion, and the blood transfusion amounts were smaller than those in the CRASH-2 trial[3,4]. The present study demonstrated a greater survival benefit in patients with less blood transfusion requirements than those in CRASH-2. In contrast, in the study[7] that demonstrated excess mortality with tranexamic acid administration, 97 per cent of the enrolled subjects received a blood transfusion.

Despite the reported association between tranexamic acid administration and reduced blood transfusion requirements in patients mainly undergoing elective surgery[2], it has been suggested that the reduction in mortality with tranexamic acid might be associated inversely with increased blood transfusion requirements in injured patients[3,4,7–10]. In particular, some investigators[25] identified a phenomenon called 'fibrinolysis shutdown' in that fibrinolysis observed on thromboelastography was highly attenuated in more than half of severely injured patients. This can theoretically explain the inconsistent effects of antifibrinolytics across studies and may suggest that tranexamic acid should be administered selectively[6,26]. However, no data have supported a statistical interaction between tranexamic acid administration and degree of fibrinolysis on clinical outcomes.

Based on the present result, the authors assume that tranexamic acid greatly benefits haemostasis in intracranial bleeding, which infrequently requires a blood transfusion, rather than extracranial bleeding. Two RCTs[27,28] have tested the survival benefit of tranexamic acid administration in patients with traumatic brain injury. The CRASH-2 Intracranial Bleeding Study[27] demonstrated a non-significant association between tranexamic acid and reduction in intracranial haemorrhage growth, fewer ischaemic lesions and lower mortality. Similarly, the second trial[28] also demonstrated non-significant associations, with reductions in haemorrhage growth and lower mortality. In addition, the PED-TRAX (Paediatric Trauma and Tranexamic Acid) study[29] not only found a significant survival benefit in injured children, but also showed

improved neurological outcomes associated with tranexamic acid administration. These studies[27–29] suggested that tranexamic acid administration might be associated with improved CT findings, and therefore might improve neurological outcome and survival in patients with traumatic brain injury. The CRASH-3 trial will test the effects of tranexamic acid for subjects with traumatic brain injury and might finally address this hypothesis[30].

A correlation between tranexamic acid administration and blood transfusion amounts was not observed here or in previous studies[3,4,7–9], except for the MATTERs study[10]. An observational study[8] found that tranexamic acid was associated with better survival for haemodynamically unstable injured patients with a base deficit of at least 6 mEq/l, who potentially require greater amounts of transfused blood. Survivor bias might explain the lack of association between blood transfusion amount and decreased mortality, because tranexamic acid administration correlated with extended survival and increased risk of blood transfusion during early trauma care[31]. However, the present study also found that tranexamic acid was not associated with blood transfusion requirements in both the overall group and 24-h survivors. Therefore, survivor bias might have a limited effect on the association between blood transfusion amounts and tranexamic acid administration. Alternatively, the authors speculate that the presence of a traumatic brain injury might explain the findings; approximately three-quarters of the propensity score-matched subjects had a traumatic brain injury, and the early administration of tranexamic acid contributed mostly to reduced mortality from a primary brain injury.

The present study has several limitations. First, the retrospective design might have limited the ability of the propensity score matching analysis to demonstrate a causal association, such as can occur with an RCT. In particular, the analyses could not be adjusted for some confounders that were unmeasured and potentially associated with the study outcome. Although instrumental variable analysis allowed for adjustment of unmeasured confounders and demonstrated consistent benefit of tranexamic acid administration for 28-day all-cause mortality, this method was not versatile in that it showed uncertainty with a much broader c.i. Second, the sample size was small, with 500 of the original 796 subjects remaining after matching. The absolute risk reduction in 28-day mortality of 8·4 per cent was large and statistically significant, but a reporting bias was possible. However, the differences in baseline characteristics of subjects in the CRASH-2 trial and those in the present study, and the incomplete randomization to treatment in the CRASH-2 trial[3–6], might have resulted in an inability to detect statistically significant differences. Finally, almost all patients (99·6 per cent) included in the propensity score matching analysis experienced a blunt injury. Therefore, it is difficult to generalize the study findings to subjects with a penetrating injury.

Collaborators

J-OCTET investigators are: M. Hayakawa, K. Maekawa (Hokkaido University Hospital, Sapporo); D. Saitoh (National Defence Medical College, Tokorozawa); H. Ogura (Osaka University Graduate School of Medicine, Osaka); J. Sasaki, T. Shibusawa (Keio University School of Medicine, Tokyo); T. Uejima (Kindai University Faculty of Medicine, Osakasayama); A. Yaguchi, M. Takeda (Tokyo Women's Medical University, Tokyo); H. Ishikura, Y. Nakamura (Fukuoka University, Fukuoka); D. Kudo (Tohoku University Graduate School of Medicine, Sendai); N. Kaneko (Fukaya Red Cross Hospital, Saitama); T. Matsuoka, Y. Hagiwara (Rinku General Medical Centre, Izumisano); N. Morimura, S. Furugori (Yokohama City University Graduate School of Medicine, Yokohama); H. Kato, T. Kanemura (National Hospital Organization Disaster Medical Centre, Tachikawa); G. Mayama (National Centre for Global Health and Medicine, Tokyo); S. Kim (Nippon Medical School, Tokyo); O. Takasu (Kurume University School of Medicine, Kurume); K. Nishiyama (Juntendo University Urayasu Hospital, Urayasu).

Acknowledgements

The authors thank Editage (www.editage.jp) for English language editing. This study was supported in part by the Japan Society for the Promotion of Science, KAKENHI (grant numbers 25462810 and 24592731).

References

1 Okamoto S, Hijikata-Okunomiya A, Wanaka K, Okada Y, Okamoto U. Enzyme controlling medicines: introduction. *Semin Thromb Hemost* 1997; **23**: 493–501.
2 Henry DA, Carless PA, Moxey AJ, O'Connell D, Stokes BJ, Fergusson DA *et al.* Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion. *Cochrane Database Syst Rev* 2011; (1)CD001886.
3 CRASH-2 trial collaborators, Shakur H, Roberts I, Bautista R, Caballero J, Coats T *et al.* 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.
4 CRASH-2 collaborators, Roberts I, Shakur H, Afolabi A, Brohi K, Coats T *et al.* The importance of early treatment with tranexamic acid in bleeding trauma patients: an

exploratory analysis of the CRASH-2 randomised controlled trial. *Lancet* 2011; **377**: 1096–1101.
5 Cap AP, Baer DG, Orman JA, Aden J, Ryan K, Blackbourne LH. Tranexamic acid for trauma patients: a critical review of the literature. *J Trauma* 2011; **71**(Suppl): S9–S14.
6 Napolitano LM, Cohen MJ, Cotton BA, Schreiber MA, Moore EE. Tranexamic acid in trauma: how should we use it? *J Trauma Acute Care Surg* 2013; **74**: 1575–1586.
7 Valle EJ, Allen CJ, Van Haren RM, Jouria JM, Li H, Livingstone AS *et al.* Do all trauma patients benefit from tranexamic acid? *J Trauma Acute Care Surg* 2014; **76**: 1373–1378.
8 Cole E, Davenport R, Willett K, Brohi K. Tranexamic acid use in severely injured civilian patients and the effects on outcomes: a prospective cohort study. *Ann Surg* 2015; **261**: 390–394.
9 Harvin JA, Peirce CA, Mims MM, Hudson JA, Podbielski JM, Wade CE *et al.* The impact of tranexamic acid on mortality in injured patients with hyperfibrinolysis. *J Trauma Acute Care Surg* 2015; **78**: 905–909.
10 Morrison JJ, Dubose JJ, Rasmussen TE, Midwinter MJ. Military Application of Tranexamic Acid in Trauma Emergency Resuscitation (MATTERs) study. *Arch Surg* 2012; **147**: 113–119.
11 Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. *Biometrika* 1983; **70**: 41–55.
12 Elm von E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP *et al.* The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet* 2007; **370**: 1453–1457.
13 Venables WN, Ripley BD. *Modern Applied Statistics with S*. Springer: New York, 2002.
14 Fox J, Weisberg W. *An R Companion to Applied Regression*. Sage: Thousand Oaks, 2011.
15 van Buuren S, Groothuis-Oudshoorn K. mice: multivariate imputation by chained equations in R. *Journal of Statistical Software* 2011; **45**: 1–67.
16 Sekhon JS. Multivariate and propensity score matching software with automated balance optimization: the matching package for R. *Journal of Statistical Software* 2011; **42**: 1–52.
17 Harrell FE Jr. *RMS: Regression Modeling Strategies. R Package Version 4.4.1*. https://CRAN.R-project.org/package=rms [accessed 29 June 2016].
18 Kleiber C, Zeileis A. *Applied Econometrics with R*. Springer: New York, 2008.
19 Robitzsch A. *Miceadds: Some Additional Multiple Imputation Functions, Especially for 'Mice'. R Package Version 1.5.0*. https://CRAN.R-project.org/package=miceadds [accessed 29 June 2016].
20 Rubin DB. Inference and missing data. *Biometrika* 1976; **63**: 581–592.
21 Rubin DB. *Multiple Imputation for Nonresponse in Surveys*. J. Wiley & Sons: New York, 1987.
22 Efron B, Tibshirani RJ. *An Introduction to the Bootstrap*. CRC Press: Boca Raton, 1993.
23 Normand ST, Landrum MB, Guadagnoli E, Ayanian JZ, Ryan TJ, Cleary PD *et al.* Validating recommendations for coronary angiography following acute myocardial infarction in the elderly: a matched analysis using propensity scores. *J Clin Epidemiol* 2001; **54**: 387–398.
24 Ilhan MN, Durukan E, Ilhan SO, Aksakal FN, Ozkan S, Bumin MA. Self-medication with antibiotics: questionnaire survey among primary care center attendants. *Pharmacoepidemiol Drug Saf* 2009; **18**: 1150–1157.
25 Moore HB, Moore EE, Gonzalez E, Chapman MP, Chin TL, Silliman CC *et al.* Hyperfibrinolysis, physiologic fibrinolysis, and fibrinolysis shutdown: the spectrum of postinjury fibrinolysis and relevance to antifibrinolytic therapy. *J Trauma Acute Care Surg* 2014; **77**: 811–817.
26 Moore EE, Moore HB, Gonzalez E, Chapman MP, Hansen KC, Sauaia A *et al.* Postinjury fibrinolysis shutdown: rationale for selective tranexamic acid. *J Trauma Acute Care Surg* 2015; **78**(Suppl 1): S65–S69.
27 CRASH-2 Collaborators (Intracranial Bleeding Study). Effect of tranexamic acid in traumatic brain injury: a nested randomised, placebo controlled trial (CRASH-2 Intracranial Bleeding Study). *BMJ* 2011; **343**: d3795.
28 Yutthakasemsunt S, Kittiwatanagul W, Piyavechvirat P, Thinkamrop B, Phuenpathom N, Lumbiganon P. Tranexamic acid for patients with traumatic brain injury: a randomized, double-blinded, placebo-controlled trial. *BMC Emerg Med* 2013; **13**: 20.
29 Eckert MJ, Wertin TM, Tyner SD, Nelson DW, Izenberg S, Martin MJ. Tranexamic acid administration to pediatric trauma patients in a combat setting: the Pediatric Trauma and Tranexamic Acid study (PED-TRAX). *J Trauma Acute Care Surg* 2014; **77**: 852–858.
30 Dewan Y, Komolafe EO, Mejía-Mantilla JH, Perel P, Roberts I, Shakur H; CRASH-3 Collaborators. CRASH-3 – tranexamic acid for the treatment of significant traumatic brain injury: study protocol for an international randomized, double-blind, placebo-controlled trial. *Trials* 2012; **13**: 87.
31 Roberts I, Preto-Merino D, Manno D. Mechanism of action of tranexamic acid in bleeding trauma patients: an exploratory analysis of data from the CRASH-2 trial. *Crit Care* 2014; **18**: 685.

Supporting information

Additional supporting information may be found in the online version of this article:

Table S1 Variables included in outlier removal and multiple imputation (Word document)

Fig. S1 Linear correlation between prothrombin time and prothrombin time international normalized ratio before and after removal of statistically significant outliers using robust regression (Word document)

Fig. S2 Linear correlation between D-dimer and fibrin degeneration product before and after removal of statistically significant outliers using robust regression (Word document)

Fig. S3 Receiver operating characteristic (ROC) curve analysis of the propensity score to predict administration of tranexamic acid (Word document)

Fig. S4 Hosmer–Lemeshow goodness-of-fit analysis between the propensity score and administration of tranexamic acid (Word document)

Fig. S5 Distribution of the propensity score before and after matching (Word document)

Fig. S6 Standardized mean differences between subjects who received tranexamic acid and controls before and after propensity score matching in imputed data sets (Word document)

Fig. S7 Standardized mean differences between subjects who received tranexamic acid and controls before and after propensity score matching in a non-imputed data set (Word document)

Fig. S8 Sensitivity analyses (Word document)

Appendix S1 Estimation and metrics of the propensity score (Word document)