Safety and efficacy of tranexamic acid in minimizing perioperative bleeding in extrahepatic abdominal surgery: meta-analysis

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Abstract

Background: Perioperative bleeding is associated with increased morbidity and mortality in patients undergoing elective abdominal surgery. The antifibrinolytic agent tranexamic acid (TXA) has been shown to reduce perioperative bleeding and mortality risk in patients with traumatic injuries, but there is a lack of evidence for its use in elective abdominal and pelvic surgery. This meta-analysis of RCTs evaluated the effectiveness and safety of TXA in elective extrahepatic abdominopelvic surgery.

Methods: PubMed, Embase, and ClinicalTrial.gov databases were searched to identify relevant RCTs from January 1947 to May 2020. The primary outcome, intraoperative blood loss, and secondary outcomes, need for perioperative blood transfusion, units of blood transfused, thromboembolic events, and mortality, were extracted from included studies. Quantitative pooling of data was based on a random-effects model.

Results: Some 19 studies reporting on 2205 patients who underwent abdominal, pelvic, gynaecological or urological surgery were included. TXA reduced intraoperative blood loss (mean difference –188.35 ml (95 per cent c.i. –254.98 to –121.72) ml) and the need for perioperative blood transfusion (odds ratio (OR) 0.43, 95 per cent c.i. 0.28 to 0.65). TXA had no impact on the incidence of thromboembolic events (OR 0.49, 0.18 to 1.35). No adverse drug reactions or in-hospital deaths were reported.

Conclusion: TXA reduces intraoperative blood loss during elective extrahepatic abdominal and pelvic surgery without an increase in complications.

Introduction

Perioperative bleeding is a major risk during and after surgery, and is associated with increases in transfusion requirements, treatment costs, morbidity and mortality.1-2 The cause of bleeding in the surgical patient is multifactorial, and can include several contributing factors such as undiagnosed and acquired coagulopathies, haemodilution, activation of fibrinolytic and inflammatory factors, and hypothermia.3,4 Perioperative bleeding is the most common indication for blood transfusion in the inpatient setting.5 Blood transfusion carries significant risks, including transfusion-related adverse reactions, infections, renal impairment, immunological incompatibility, and even death.6-7

Tranexamic acid (TXA) is a synthetic lysine analogue that reduces the risk of haemorrhage by inhibition of plasmin activity and therefore fibrinolysis.8 Its antifibrinolytic properties were first described in 1966.9 Its effectiveness in reducing perioperative blood loss and improving outcomes have been described in trauma,10-11 and orthopaedic surgery12-13, resulting in its incorporation into the standard of care.14 It is a safe drug with minimal serious side-effects even at high doses and with long-term use.15 TXA is inexpensive, costing €20 for a single dose, whereas a single blood transfusion can cost up to €170.16

Although evidence exists for its use in trauma,10,11 there is a lack of data showing benefit in elective abdominal and pelvic procedures, which are often associated with high risks of surgical bleeding.17,18 A Cochrane review15 in 2011 evaluated three antifibrinolytic agents, including aprotinin, TXA, and ε-aminocaproic acid, in elective surgery. Of the 53 trials included in that review reporting on TXA use, only three involved elective abdominal or pelvic surgery. Current National Institute for Health and Care Excellence guidelines recommend the administration of perioperative TXA in procedures with a reasonable likelihood of moderate blood loss (quantified as 500 ml), but of the 25 trials reviewed only four studies in abdominal or pelvic surgery, the majority were studies in orthopaedic, cardiac, and head and neck surgery.47 In these trials, TXA was given topically, orally or intravenously, and at a variety of doses. Whether these results can be extrapolated to cover all of elective abdominal surgery is debatable. The recently published HALT-IT trial concluded that TXA was not beneficial for gastrointestinal bleeding, suggesting that the pathophysiology of bleeding may well be specific to the patient population and setting.

The aim of this systematic review was to evaluate the efficacy and safety of TXA in elective extrahepatic abdominal and pelvic surgery based on the results from RCTs.
Methods
This systematic review was conducted according to the PRISMA statement.

Search strategy
A systematic search of MEDLINE, Embase, PubMed, and ClinicalTrials.gov databases was undertaken to identify relevant studies from January 1947 to May 2020. Medical Subject Heading (MeSH) terms and keywords relating to TXA in perioperative bleeding were combined with terms relating to gastrointestinal, urological, and gynaecological surgery, ['tranexamic acid'] AND ['perioperative' OR 'intraoperative' OR 'postoperative' AND 'haemorrhage'] AND ['abdominal surgery' or 'pelvic surgery'] (Table S1). Cochrane Handbook search filters were used to identify RCTs using the sensitivity-maximizing filter. The bibliographies of all studies that met the inclusion criteria were hand-searched for additional articles to ensure comprehensive study inclusion.

Inclusion criteria
The review included RCTs evaluating the use of perioperative systemic TXA (oral or intravenous) administered to any patients undergoing elective abdominal extrahepatic surgery. This included extrahepatic gastrointestinal, vascular, urological, and gynaecological procedures. Comparator groups of interest included standard of care, placebo or no intervention. Studies had to include human subjects aged 18 years or older; only those published in English were considered.

Exclusion criteria
Case reports, observational studies, letters, systematic reviews, and meta-analyses were excluded. RCTs evaluating antifibrinolytics other than TXA were excluded from analysis. Studies in which TXA was not the sole agent and those that lacked a comparator group were excluded. RCTs evaluating TXA in hepatic, skeletal, non-abdominal, non-surgical, and emergency or trauma procedures were not examined.

Study selection and data extraction
Studies were screened based on title and abstract. Those meeting the eligibility criteria were read in full. Two reviewers independently assessed the full texts of the retrieved studies to ensure they met the inclusion criteria, with discordance resolved by consensus.

Fig. 1 PRISMA diagram showing selection of articles for review
Study characteristics and outcomes were documented using a standardized data extraction form. This included information regarding randomization, blinding, methodology, type of surgical procedure, target population, and treatment outcomes. The following data were reported for each selected study: year of publication, authors, study characteristics, inclusion and exclusion criteria, dose and timing of TXA administration, description of control group, and sample size.

The primary outcome was intraoperative blood loss, and secondary outcomes were need for perioperative blood transfusion, thromboembolic events, and mortality.

For the purpose of statistical analysis, the procedures were grouped into abdominal (urology, general and vascular surgery) and pelvic (obstetrics and gynaecology) operations.

Assessment of risk of bias
Studies that met the inclusion criteria were assessed for risk of bias using the Cochrane Collaboration’s tool. The following domains were assessed for each study: selection bias, performance bias, detection bias, attrition, and reporting bias. A risk-of-bias table was completed using Review Manager (RevMan version 5.4) software (The Nordic Cochrane Centre, Copenhagen, Denmark).

Statistical analysis
Meta-analyses of the pooled data were performed using RevMan version 5.4. Effects for dichotomous outcomes were summarized as odds ratios (ORs) with 95 per cent confidence intervals. For continuous outcomes, the results were presented as weighted mean differences (MDs) with 95 per cent confidence intervals. Statistical heterogeneity of the included studies was measured by using the $I^2$ statistic, with upper limits of 25, 50 and 75 per cent considered to represent statistically low, moderate, and high levels of heterogeneity respectively. Publication bias was assessed as described by Eggers and colleagues, using visual inspection for asymmetry of the funnel plot based on the primary outcome.

Protocol registration
The protocol for this systematic review was registered with Open Science Framework Registries.

Results
Study selection
A total of 533 studies were retrieved (Fig. 1) with a further 15 studies identified by hand-searching. After excluding duplicates, 479 abstracts were reviewed, and 20 full publications identified as potentially eligible. After critical appraisal of the studies, one was excluded owing to ambiguous randomization techniques, leaving 19 RCTs that met the eligibility criteria with a total of 2205 participants (1119 TXA, 1086 control).

Study characteristics
Included studies were published between 2008 and 2020 (Table 1). There were seven trials from Asia, seven from the Middle East, four from Europe, and one from Africa. Trials included procedures in vascular surgery (1), urology

| Reference | Study interval | Setting | No. of participants | Surgery type | Procedure(s) performed |
|-----------|----------------|---------|---------------------|--------------|-----------------------|
| Monaco et al. 50 | 2015–2018 | Italy (single centre) | 100 | Vascular | Open repair of AAA |
| Abbas et al. 62 | 2016–2017 | Egypt (single centre) | 62 | Obstetrics | Caesarean section |
| Abdul et al. 56 | 2017–2018 | Nigeria (single centre) | 80 | Gynaecology | Abdominal myomectomy |
| Sallam and Shady 57 | 2015–2017 | Egypt (single centre) | 86 | Gynaecology | Abdominal hysterectomy |
| Prasad et al. 53 | Unknown | India | 60 | General Surgery | Bilateral adrenalectomy |
| Shady et al. 58 | 2015–2017 | Egypt (single centre) | 70 | Gynaecology | Abdominal myomectomy |
| Alhomoud 54 | 2014 | Kuwait (single centre) | 50 | General surgery | Laparoscopic sleeve gastrectomy |
| Sujata et al. 63 | 2012–2013 | India (single centre) | 60 | Obstetrics | Caesarean section |
| Topsoe et al. 59 | 2013–2014 | Denmark (4 centres) | 332 | Gynaecology | Hysterectomy |
| Lundin et al. 60 | 2008–2012 | Sweden (4 centres) | 100 | Gynaecology | Open radical debulking surgery for ovarian cancer |
| Goswami et al. 64 | 2009–2011 | India (single centre) | 90 | Obstetrics | Caesarean section |
| Kumar et al. 51 | 2011–2012 | India (single centre) | 200 | Urology | Percutaneous nephrolithotomy |
| Sentürk et al. 65 | 2010 | Turkey (single centre) | 223 | Obstetrics | Caesarean section |
| Shahid and Khan 66 | 2009–2011 | Pakistan (single centre) | 74 | Obstetrics | Caesarean section |
| Xu et al. 67 | 2008–2011 | China (single centre) | 174 | Obstetrics | Biliary tract surgical procedures |
| Pfizer 51 | 2009–2011 | India (single centre) | 44 | General surgery | Pancreatoduodenectomy |
| Crescenti et al. 52 | 2008–2010 | Italy (single centre) | 200 | Urology | Oesophagectomy |
| Movafegh et al. 68 | 2009–2010 | Iran (single centre) | 100 | Obstetrics | Colectomy |
| Caglar et al. 51 | 2004 | Turkey (single centre) | 100 | Gynaecology | Gastroctomy |

The study recruited 129 patients; however only 86 were eligible for inclusion in this current analysis. *AAA, abdominal aortic aneurysm.
A Mantel–Haenszel random-effects model was used for meta-analysis. Odds ratios are shown with 95 per cent confidence intervals. TXA, tranexamic acid.

**Fig. 2** Meta-analysis of the effect of tranexamic acid on intraoperative blood loss
An inverse-variance random-effects model was used for meta-analysis. Mean differences are shown with 95 per cent confidence intervals. *values are mean(s.d.). TXA, tranexamic acid.

| Reference | Blood transfusion | Transfusion | Odds ratio | Odds ratio |
|-----------|-------------------|-------------|------------|------------|
| Pelvic surgery | TXA | Control | Weight (%) | Odds ratio | Odds ratio |
| Abdul et al.66 | 12 of 40 | 18 of 40 | 10.6 | 0.52 (0.21, 1.31) | |
| Sallam and Shady57 | 1 of 43 | 4 of 43 | 3.0 | 0.23 (0.02, 2.17) | |
| Shady et al.58 | 6 of 35 | 19 of 35 | 8.6 | 0.17 (0.06, 0.52) | |
| Sujita et al.69 | 1 of 30 | 4 of 30 | 2.9 | 0.22 (0.02, 2.14) | |
| Topsoee et al.70 | 2 of 166 | 7 of 167 | 5.2 | 0.28 (0.06, 1.37) | |
| Lundin et al.71 | 15 of 50 | 22 of 50 | 11.6 | 0.55 (0.24, 1.24) | |
| Shahid and Khan60 | 3 of 38 | 12 of 36 | 6.5 | 0.17 (0.04, 0.67) | |
| Goswami et al.72 | 0 of 60 | 2 of 30 | 1.7 | 0.09 (0.00, 2.03) | |
| Sentürk et al.73 | 0 of 101 | 0 of 122 | Not estimable | |
| Caglar et al.74 | 15 of 50 | 10 of 50 | 10.6 | 1.71 (0.68, 4.30) | |
| Subtotal | 55 of 612 | 98 of 603 | 60.9 | 0.39 (0.21, 0.72) | |

Heterogeneity: $\chi^2 = 0.37; \chi^2 > 15.25, 8 \text{ d.f.}, P < 0.05; I^2 = 48%$
Test for overall effect: $Z = 3.02, P = 0.003$

| Abdominal surgery | TXA | Control | Weight (%) | Odds ratio | Odds ratio |
|-------------------|-----|---------|------------|------------|------------|
| Monaco et al.75 | 7 of 50 | 12 of 50 | 9.3 | 0.52 (0.18, 1.44) | |
| Prasad et al.76 | 2 of 40 | 4 of 20 | 4.3 | 0.21 (0.03, 1.27) | |
| Kumar et al.77 | 2 of 100 | 11 of 100 | 5.5 | 0.17 (0.04, 0.77) | |
| Pfizer78 | 5 of 23 | 3 of 21 | 5.3 | 1.67 (0.35, 8.04) | |
| Crescenti et al.79 | 22 of 100 | 37 of 100 | 14.7 | 0.48 (0.26, 0.90) | |
| Subtotal | 38 of 313 | 67 of 291 | 39.1 | 0.46 (0.26, 0.82) | |

Heterogeneity: $\chi^2 = 0.10; \chi^2 > 5.09, 4 \text{ d.f.}, P = 0.28; I^2 = 21%$
Test for overall effect: $Z = 2.65, P = 0.008$

| Total | 93 of 925 | 165 of 894 | 100.0 | 0.43 (0.28, 0.65) | |

Heterogeneity: $\chi^2 = 0.20; \chi^2 > 20.34, 13 \text{ d.f.}, P = 0.09; I^2 = 36%$
Test for overall effect: $Z = 4.02, P < 0.0001$
Test for subgroup differences: $\chi^2 = 0.14, 1 \text{ d.f}, P = 0.71, I^2 = 0%$

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**Fig. 3** Meta-analysis of the effect of tranexamic acid on the need for blood transfusion
A Mantel–Haenszel random-effects model was used for meta-analysis. Odds ratios are shown with 95 per cent confidence intervals. TXA, tranexamic acid.
Description of dose regimen

In 13 of 19 trials, TXA was given as a single bolus before operation (Table S2). In the other trials, it was administered as a bolus before surgery followed by a continuous infusion (4 trials), or as a preoperative bolus with subsequent additional doses (2 trials). The most common TXA dosing was based on patient weight (11 of 19 trials).

TXA was compared with placebo in 16 trials, and normal standard of care in three. Two trials\(^53,64\) had three arms, whereby the authors compared two TXA doses with placebo. For the purpose of this analysis, data from the two TXA subgroups were combined to allow a pooled comparison of outcomes between patients receiving TXA and control, irrespective of dosage.

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**Meta-analysis**

**Intraoperative blood loss**

Twelve studies\(^50,52,55–59,61,62,66–68\) reported the effect of TXA on intraoperative blood loss (Fig. 2). Compared with the control group, TXA had a statistically significant effect in reducing intraoperative blood loss (MD \(-188.35\) (95 per cent c.i. \(-254.98\) to \(-121.72\)) ml), albeit with significant heterogeneity between studies (\(I^2 = 89\) per cent). In separate analyses of abdominal and pelvic surgery, there was acceptable heterogeneity in intraoperative blood loss in the abdominal group (\(I^2 = 11\) per cent). Statistical heterogeneity for the pelvic group remained substantial (\(I^2 = 92\) per cent).

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**Fig. 4 Meta-analysis of the effect of tranexamic acid on units of blood transfused**

An inverse-variance random-effects model was used for meta-analysis. Mean differences are shown with 95 per cent confidence intervals. *values are mean(s.d.). TXA, tranexamic acid.

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**Fig. 5 Meta-analysis of the effect of tranexamic acid on thromboembolic events**

A Mantel–Haenszel random-effects model was used for meta-analysis. Odds ratios are shown with 95 per cent confidence intervals. TXA, tranexamic acid.
Need for perioperative blood transfusion

Fifteen studies\textsuperscript{50–53,55–61,63–66} reported on the need for perioperative blood transfusion (Fig. 3). TXA significantly reduced the proportion of patients requiring a transfusion (OR 0.43, 95 per cent c.i. 0.28 to 0.65), with acceptable statistical heterogeneity across all surgery types, with and without subgroup analyses (overall $I^2 = 36$ per cent).

Unit volume of blood transfused

Only four studies\textsuperscript{52,56,60,61} reported on the unit volume of blood transfused (Fig. 4). Administration of TXA did not affect the volume of blood transfused (MD $-0.16$ (95 per cent c.i. $-0.56$ to 0.25) units).

Thromboembolic events

Of 15 studies\textsuperscript{50–57,59–61,64–67} that reported on thromboembolic complications (Fig. 5), 12 had no thromboembolic events in either arm. Of the three trials that found thromboembolic events, there was no statistical difference between the TXA and control groups (OR 0.49, 95 per cent c.i. 0.18 to 1.35).

Mortality

Only five studies\textsuperscript{50,52,57,59,67} considered mortality as an outcome. The duration of follow-up in these studies ranged from the hospital admission to 1 year. There were no deaths reported in any study.

Risk of bias

Overall, five trials had a low risk, six a high risk, and eight an unclear risk of bias (Fig. 6). The random sequence generation was adequate in 14 trials, whereas the allocation was concealed adequately in 12. Risk of bias for blinding was adequate in seven trials.

Of the 12 studies reporting intraoperative blood loss, five had a low risk of blinding bias, three had a high risk, and four an unclear risk. The risk of bias of blinding was similar in studies that reported the need for transfusion (6 studies low risk, 4 studies high risk, and 5 studies unclear risk) and thromboembolic events (6 studies low risk, 4 studies high risk, and 5 studies unclear risk).

Discussion

This meta-analysis found that preoperative TXA in extrahepatic abdominal and pelvic operations reduced intraoperative blood loss and the need for perioperative blood transfusion, with no increased risk of postoperative thromboembolic events. TXA had no discernible impact on mortality, although this was limited by the small number of studies reporting death as an outcome and variation in duration of follow-up.

Although there was substantial heterogeneity between the studies regarding the overall analysis of intraoperative blood loss, this was partially resolved by subgroup analysis. The pelvic (obstetrics and gynaecology) subgroup continued to show heterogeneity, probably reflecting differences in clinical populations. Despite this, effect estimates in each of the trials consistently favoured TXA. In addition, the need for perioperative blood transfusion was significantly reduced, with little variation in outcomes between the different types of surgery.

The reported incidence of postoperative thromboembolic event was low in this analysis, with the majority of trials reporting no events at all. The small number of events seen in three studies\textsuperscript{52,60,67}, even with follow-up of up to 6 months, supports the safety of TXA.

The use of TXA in patients with bleeding from traumatic injuries became firmly established after the CRASH-2 trial\textsuperscript{11}. The multicentre WOMAN trial\textsuperscript{69} also reported a reduced risk of death when TXA was given in women with postpartum haemorrhage, further supporting its efficacy in reducing traumatic or surgical bleeding. Despite similarities in haemostatic responses, including...
fibrinolysis, between major surgery and trauma, few studies have investigated TXA in elective abdominal surgery. This systematic review has shown that TXA reduces perioperative bleeding and the need for blood transfusion in elective extrahepatic abdominal surgery.

A recent systematic review evaluated the effect of TXA on the need for perioperative blood transfusion across a range of surgical specialties in both emergency and elective settings. Owing to the wide inclusion of surgical specialties with varying degrees of urgency, there was significant statistical heterogeneity between studies. Despite this, effect estimates in that analysis support the present findings regarding the need for perioperative blood transfusion and all-cause mortality.

The recently published HALT-IT trial concluded that TXA did not reduce blood loss, need for transfusion or mortality after an acute upper gastrointestinal bleed, but was associated with a significant risk of venous thromboembolism (VTE). These results contradict those from trauma and orthopaedic settings, emphasizing that the pathophysiology of bleeding varies and the hazard of extrapolating outcomes from one patient population to another.

There remains uncertainty regarding the risk of thromboembolic events with TXA. In the present review, the majority of studies reported symptomatic VTEs. Only one study reported both symptomatic and asymptomatic VTEs evident on delayed surveillance, so there may have been an underdiagnosis of postoperative VTEs. The importance of asymptomatic VTEs in elective extrahepatic abdominopelvic surgery, however, remains unknown. In the HALT-IT trial, which identified a significant risk of VTE in those receiving TXA, a significant proportion of the patients had liver disease and cirrhosis, and these may be important confounders. A systematic review that evaluated the basis of exclusion of patients in trials evaluating TXA found, based on 161 studies and a total of 20,679 patients, no increased risk of VTEs from systemic TXA compared with placebo or no intervention (risk ratio 0.95, 95 per cent c.i. 0.78 to 1.15).

The present analysis has limitations. Although this evaluation of TXA in elective abdominopelvic surgery included 19 RCTs and 2205 patients, the individual studies were relatively small. Variation in study protocols, including differences in the dosage, rate, and timing of administration of TXA, existed and not all studies used weight-based dosing of TXA. The timing of administration of TXA ranged from 30 min before operation to the exact moment of knife to skin, and two studies did not specify the timing of TXA administration.

The threshold used by the study investigators for the need for perioperative blood transfusion differed across the 15 studies. Two trials relied on clinicians’ subjective decision, whereas seven did not describe a protocol for triggering transfusions, and only six relied on a fall in haemoglobin levels or clinically significant hypotensive episodes.

Duration of follow-up was variable. Trials with shorter follow-up may have under-reported postoperative complications. Most studies focused on clinically significant VTEs, and only one reported asymptomatic VTEs. Follow-up limited to time of hospital discharge is known to capture thromboembolic events inadequately. Procedure-specific analysis was not feasible given the limited number of studies included.

There remains a need for larger pragmatic clinical trials evaluating the effect of TXA in patients undergoing elective abdominal surgery. Pooled analysis in this review suggested that 12 (95 per cent c.i. 7 to 16) per cent of patients in the TXA group and 23 (15 to 31) per cent in the control group needed blood transfusion. This would require a well powered RCT to recruit 372 patients (186 in each arm with a 1:1 ratio) to confirm this difference, with a power of 80 per cent and 5 per cent error margin. Despite the limitations of individual studies, such a trial seems justified as the present analysis indicated that TXA significantly reduced intraoperative blood loss and the need for blood transfusion in elective extrahepatic abdominal and pelvic surgery, without an increase in the incidence of symptomatic thromboembolic events.

Disclosure. The authors declare no conflict of interest.

Supplementary material
Supplementary material is available at BJS Open online.

References

1. Shah A, Palmer AJR, Klein AA. Strategies to minimize intraoperative blood loss during major surgery. Br J Surg 2020; 107: e26–e38
2. Pabinger I, Fries D, Schochl H, Streif W, Toller W. Tranexamic acid for treatment and prophylaxis of bleeding and hyperfibrinolysis. Wien Klin Wochenschr 2017; 129: 303–316
3. Sniecinski RM, Chandler WL. Activation of the hemostatic system during cardiopulmonary bypass. Anesth Analg 2011; 113:1319–1333
4. Despotis GJ, Avidan MS, Hogue CW. Mechanisms and attenuation of hemostatic activation during extracorporeal circulation. Ann Thorac Surg 2001; 172:S1821–S1831
5. Houston BL, Uminski K, Mutter T, Rimmer E, Houston DS, Menard CE et al. Efficacy and safety of tranexamic acid in major non-cardiac surgeries at high risk for transfusion: a systematic review and meta-analysis. Transfus Med Rev 2020; 34: 51–62
6. Delaney M, Wendel S, Bercovitz RS, Cid J, Cohn C, Dunbar NM et al. Transfusion reactions: prevention, diagnosis, and treatment. Lancet 2016; 388: 2825–2836
7. Clevenger B, Kelleher A. Hazards of blood transfusion in adults and children. Contin Educ Anaesth Crit Care Pain 2014; 14: 112–118
8. Yates J, Perelman I, Khar S, Taylor J, Lampron J, Timmoun A et al. Exclusion criteria and adverse events in perioperative trials of tranexamic acid: a systematic review and meta-analysis. Transfusion 2019; 59: 806–824
9. Kobayashi T, Sugira J. The effect of a new potent antifibrinolytic agent, tranexamic acid. J Jpn Obstet Gynecol Soc 1966; 13: 158–167
10. Perel P, Ker K, Uribe M, Roberts CH I. Tranexamic acid for reducing mortality in emergency and urgent surgery. Cochrane Database Syst Rev 2013;(1)CD010245
11. 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
12. Jennings JD, Solarz MK, Haydel C. Application of tranexamic acid in trauma and orthopedic surgery. Orthop Clin North Am 2016; 47: 137–143
13. Walterscheid Z, O’Neill C, Carmouche J. Tranexamic acid in adult elective orthopaedic and complex spinal surgery: a review. Surg Rehabil 2017; 1: 1–4
14. Binz S, McCollester J, Thomas S, Miller J, Pohlman T, Waxman D et al. CRASH-2 study of tranexamic acid to treat bleeding in trauma patients: a controversy fueled by science and social media. J Blood Transfus 2015; 2015: 1–12

Koh et al. | 7

Supplementary material is available at BJS Open online.

References

1. Shah A, Palmer AJR, Klein AA. Strategies to minimize intraoperative blood loss during major surgery. Br J Surg 2020; 107: e26–e38
2. Pabinger I, Fries D, Schochl H, Streif W, Toller W. Tranexamic acid for treatment and prophylaxis of bleeding and hyperfibrinolysis. Wien Klin Wochenschr 2017; 129: 303–316
3. Sniecinski RM, Chandler WL. Activation of the hemostatic system during cardiopulmonary bypass. Anesth Analg 2011; 113:1319–1333
4. Despotis GJ, Avidan MS, Hogue CW. Mechanisms and attenuation of hemostatic activation during extracorporeal circulation. Ann Thorac Surg 2001; 172:S1821–S1831
5. Houston BL, Uminski K, Mutter T, Rimmer E, Houston DS, Menard CE et al. Efficacy and safety of tranexamic acid in major non-cardiac surgeries at high risk for transfusion: a systematic review and meta-analysis. Transfus Med Rev 2020; 34: 51–62
6. Delaney M, Wendel S, Bercovitz RS, Cid J, Cohn C, Dunbar NM et al. Transfusion reactions: prevention, diagnosis, and treatment. Lancet 2016; 388: 2825–2836
7. Clevenger B, Kelleher A. Hazards of blood transfusion in adults and children. Contin Educ Anaesth Crit Care Pain 2014; 14: 112–118
8. Yates J, Perelman I, Khar S, Taylor J, Lampron J, Timmoun A et al. Exclusion criteria and adverse events in perioperative trials of tranexamic acid: a systematic review and meta-analysis. Transfusion 2019; 59: 806–824
9. Kobayashi T, Sugira J. The effect of a new potent antifibrinolytic agent, tranexamic acid. J Jpn Obstet Gynecol Soc 1966; 13: 158–167
10. Perel P, Ker K, Uribe M, Roberts CH I. Tranexamic acid for reducing mortality in emergency and urgent surgery. Cochrane Database Syst Rev 2013;(1)CD010245
11. 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
12. Jennings JD, Solarz MK, Haydel C. Application of tranexamic acid in trauma and orthopedic surgery. Orthop Clin North Am 2016; 47: 137–143
13. Walterscheid Z, O’Neill C, Carmouche J. Tranexamic acid in adult elective orthopaedic and complex spinal surgery: a review. Surg Rehabil 2017; 1: 1–4
14. Binz S, McCollester J, Thomas S, Miller J, Pohlman T, Waxman D et al. CRASH-2 study of tranexamic acid to treat bleeding in trauma patients: a controversy fueled by science and social media. J Blood Transfus 2015; 2015: 1–12
15. Roberts I, Shakur H, Coats T, Hunt B, Balogun E, Barnetson L et al. The CRASH-2 trial: a randomised controlled trial and economic evaluation of the effects of tranexamic acid on death, vascular occlusive events and transfusion requirement in bleeding trauma patients. Health Technol Assess 2013;17:79

16. National Institute for Health and Care Excellence. Blood Transfusion. NICE guideline NG24. https://www.nice.org.uk/guidance/ng24 (accessed 10 June 2020)

17. Mehdi Z, Birns J, Partridge J, Bhalla A, Dhesi J. Perioperative management of adult patients with a history of stroke or transient ischaemic attack undergoing elective non-cardiac surgery. Clin Med 2016;16:535–540

18. Clark NP, Douketis JD, Hasselblad V, Schulman S, Kindzelski AL, Ortel TL. Predictors of perioperative major bleeding in patients who interrupt warfarin for an elective surgery or procedure: analysis of the BRIDGE trial. Am Heart J 2018;195:108–114

19. 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;(3):CD001886

20. National Institute for Health and Care Excellence. Appendix A: Summary of Evidence from Surveillance. 2020 Surveillance of Blood Transfusion (2019) NICE Guideline NG24. https://www.nice.org.uk/guidance/ng24/evidence/appendix-a-summary-of-evidence-from-surveillance-pdf-7088309966 (accessed 10 June 2020)

21. Bansal A, Arora A. A double-blind, placebo-controlled randomized clinical trial to evaluate the efficacy of tranexamic acid in irrigant solution on blood loss during percutaneous nephrolithotomy: a pilot study from tertiary care center of North India. World J Urol 2017;35:1233–1240

22. Shaaban MM, Ahmed MR, Farhan RE, Dardeer HH. Efficacy of tranexamic acid on myomectomy-associated blood loss in patients with multiple myomas: a randomized controlled clinical trial. Reprod Sci 2016;23:908–912

23. Mohammadi Sichani M, Kazemi R, Nouri-Mahdavi K, GholiPour FR. Evaluation of the efficacy of tranexamic acid in reducing blood loss in percutaneous nephrolithotomy: a randomized clinical trial. Minerva Urol Nefrol 2019;71:55–62

24. Kietpeerakool C, Supokan A, Laopaiboon M, Lumbiganon P. Effectiveness of tranexamic acid in reducing blood loss during cysteroductive surgery for advanced ovarian cancer. Cochrane Database Syst Rev 2016;(1):CD011732

25. Chen F, Jiang Z, Li M, Zhu X. Efficacy and safety of perioperative tranexamic acid in elderly patients undergoing trochanteric fracture surgery: a randomised controlled trial. Hong Kong Med J 2019;25:120–126

26. Drakos A, Raoulis V, Karatzios K, Doxariotis N, Kontogeorgos V, Malizos K et al. Efficacy of local administration of tranexamic acid for blood salvage in patients undergoing intertrochanteric fracture surgery. J Orthop Trauma 2016;30:409–414

27. Cvetanovich GL, Fillingham YA, O’Brien M, Forsythe B, Cole BJ, Verma NN et al. Tranexamic acid reduces blood loss after primary shoulder arthroplasty: a double-blind, placebo-controlled, prospective, randomized controlled trial. JSES Open Access 2018;2:23–27

28. Fraval A, Effeney P, Fiddelaers L, Smith B, Towell B, Tran P. OBTAIN A: outcome benefits of tranexamic acid in hip arthroplasty. a randomized double-blinded controlled trial. J Arthroplasty 2017;32:1516–1519

29. Tavares Sánchez-Monge FJ, Aguado Maestro I, Bañuelos Díaz A, Martín Ferrero MA, García Alonso MF. Efficacy and safety of the topical application of tranexamic acid in cementless hip arthroplasty: prospective, randomised, double-blind and controlled study. Rev Esp Cir Ortop Traumatol 2018;62:47–54

30. Vara AD, Koueiter DM, Pinkas DE, Gowda A, Wiater BP, Wiater JM. Intravenous tranexamic acid reduces total blood loss in reverse total shoulder arthroplasty: a prospective, double-blinded, randomized, controlled trial. J Shoulder Elbow Surg 2017;26:1383–1389

31. Gillespie R, Shishani Y, Joseph S, Streit JJ, Gobeze R. Neer Award 2015: a randomized, prospective evaluation on the effectiveness of tranexamic acid in reducing blood loss after total shoulder arthroplasty. J Shoulder Elbow Surg 2015;24:1679–1684

32. Wang JW, Chen B, Lin PC, Yen SH, Huang CC, Kuo FC. The efficacy of combined use of rivaroxaban and tranexamic acid on blood conservation in minimally invasive total knee arthroplasty a double-blind randomized, controlled trial. J Arthroplasty 2017;32:801–806

33. Watts CD, Houdek MT, Sems SA, Cross WW, Pagnino MW. Tranexamic acid safely reduced blood loss in hemi- and total hip arthroplasty for acute femoral neck fracture: a randomized clinical trial. J Orthopa Trauma 2017;31:345–351

34. Wu J, Feng S, Chen X, Lv Z, Qu Z, Chen H et al. Intra-articular injection of tranexamic acid on perioperative blood loss during unicompartmental knee arthroplasty. Med Sci Monit 2019;25:5068–5074

35. Zeng Y, Si HB, Shen B, Yang J, Zhou Z, Kang P et al. Intravenous combined with topical administration of tranexamic acid in primary total hip arthroplasty: a randomized controlled trial. Orthop Surg 2019;9:174–179

36. Jordan M, Aguilera X, González JC, Castillón P, Salomón M, Hernández JA et al., TRANEXFER Group. Prevention of postoperative bleeding in hip fractures treated with prosthetic replacement: efficacy and safety of fibrin sealant and tranexamic acid. A randomised controlled clinical trial (TRANEXFER study). Arch Orthop Trauma Surg 2019;139:597–604

37. Zhou X, Zhang Y, Jiang L, Zhang J, Zhou D, Wu L et al. Efficacy and safety of tranexamic acid in intertrochanteric fractures: a single-blind randomized controlled trial. Orthop Surg 2019;11:635–642

38. Mohib Y, Rashid R, Ali M, Zubiari A, Umer M. Does tranexamic acid reduce blood transfusion following surgery for intertrochanteric fracture? A randomised control trial. J Pakistan Med Assoc 65(Suppl 3):S17–S20

39. Mu X, Wei J, Wang C, Ou Y, Yin D, Liang B et al. Intravenous administration of tranexamic acid significantly reduces visible and hidden blood loss compared with its topical administration for double-segment posterior lumbar interbody fusion: a single-center, placebo-controlled randomized trial. World Neurosurg 2019;122:e821–e827

40. Goobie SM, Zurakowski D, Glotzbecker MP, McCann ME, Hedequist D, Brustowicz RM et al. Tranexamic acid is efficacious at decreasing the rate of blood loss in adolescent scoliosis surgery: a randomized placebo-controlled trial. J Bone Joint Surg 2018;100:2014–2032

41. Aguilera X, Martinez-Zapata MJ, Hinarcejos P, Jordán M, Leal J, González JC et al. Topical and intravenous tranexamic acid reduce blood loss compared to routine hemostasis in total knee arthroplasty: a multicenter, randomized, controlled trial. Arch Orthop Trauma Surg 2015;135:1017–1025

42. Chen X, Cao X, Yang C, Guo K, Zhu Q, Zhu J. Effectiveness and safety of fixed-dose tranexamic acid in simultaneous bilateral total knee arthroplasty: a randomized double-blind controlled trial. J Arthroplasty 2016;31:2471–2475
43. Clavé A, Gérard R, Lacroix J, Baynat C, Danguy Des Déserts M, Gatineau F et al. A randomized, double-blind, placebo-controlled trial on the efficacy of tranexamic acid combined with rivaroxaban-thromboprophylaxis in reducing blood loss after primary cementless total hip arthroplasty. Bone Joint J 2019;101-B:207–212

44. Shady NW, Fervaz P, Ilyas S, Niaz M. Topical use of tranexamic acid in open heart surgery. J Pakistan Med Assoc 2018;68:538–542

45. Kulkarni AP, Chaukar DA, Patil VP, Metgudmath RB, Hawaldar A et al. Effects of a high-dose 24-h infusion of tranexamic acid on death and thromboembolic events in patients with acute gastrointestinal bleeding (HALT-IT): an international randomized, double-blind, placebo-controlled trial. Lancet 2020;395:1927–1936

46. Melsen WG, Bootsma MC, Rovers MM, Bonten MJ. The effects of a high-dose 24-h infusion of tranexamic acid versus open myomectomy with intravenous bolus tranexamic acid to reduce blood loss in abdominal oncosurgical procedures: a double-blind randomised controlled trial. J Obstet Gynecol Reprod Biol 2019;38:173–179

47. Abdul IF, Amadu MB, Adesina KT, Olarinoye AO, Omokanye LO. Adjunctive use of tranexamic acid to tourniquet in reducing haemorrhage during abdominal myomectomy—a randomized controlled trial. Eur J Obstet Gynecol Reprod Biol 2019;242:150–158

48. Shady NW, Sallam HF, Shady NW. Reducing blood loss during abdominal hysterectomy with intravenous versus topical tranexamic acid: a double-blind randomized controlled trial. J Obstet Gynecol India 2019;69:173–179

49. Shady NW, Sallam HF, Fahmy H. Reducing blood loss during open myomectomy with intravenous versus topical tranexamic acid: a double-blinded randomized placebo-controlled trial. Middle East Fertil Soc J 2018;23:225–231

50. Topsoe MF, Bergholt T, Ravn P, Schouenborg L, Moeller C, Ottesen B et al. Anti-hemorrhagic effect of prophylactic tranexamic acid in benign hysterectomy—a double-blinded randomized placebo-controlled trial. Am J Obstet Gynecol 2016;215:72.e1–e8

51. Kulkarni AP, Chaukar DA, Patil VP, Metgudmath RB, Hawaldar A et al. Effects of a high-dose 24-h infusion of tranexamic acid on death and thromboembolic events in patients with acute gastrointestinal bleeding (HALT-IT): an international randomized, double-blind, placebo-controlled trial. Lancet 2020;395:1927–1936

52. Melsen WG, Bootsma MC, Rovers MM, Bonten MJ. The effects of a high-dose 24-h infusion of tranexamic acid versus open myomectomy with intravenous bolus tranexamic acid to reduce blood loss in abdominal oncosurgical procedures: a double-blind randomised controlled trial. J Obstet Gynecol Reprod Biol 2019;38:173–179

53. Alhomoud H. The effect of tranexamic acid on blood loss during cesarean delivery. J Gynecol Obstet Hum Reprod 2013;42:115–119

54. Alhomoud H. The effect of tranexamic acid on blood loss during cesarean delivery. J Gynecol Obstet Hum Reprod 2013;42:115–119

55. Prasad R, Patki A, Padhy S, Ramchandran G. Single intravenous dose of tranexamic acid reduces blood loss during and after caesarean section. J Obstet Gynaecol India 2013;67:225–231

56. Sentürk MB, Cakmak Y, Yildiz G, Yildiz P. Tranexamic acid for the prevention of postpartum hemorrhage undergong cesarean delivery. Int J Gynecol Obstet 2016;133:312–315

57. Shahid A, Khan A. Tranexamic acid in decreasing blood loss during and after caesarean section. J Coll Physicians Surg Pak 2013;23:459–462

58. Xu J, Gao W, Ju Y. Tranexamic acid for the prevention of postpartum hemorrhage after cesarean section: A double-blind randomized controlled trial. Am J Obstet Gynecol 2019;221:48:e1–e8

59. Amin AN, Lenhart G, Princic N, Lin J, Thompson S, Johnston S. Retrospective administrative database study of the time period of venous thromboembolism risk during and following hospitalization for major orthopedic or abdominal surgery in real-world US patients. Hosp Pract 2011;39:7–16

60. Sweetland S, Green J, Liu B, Berrington de González A, Canonico M, Reeves G et al.; Million Women Study Collaborators. Duration and magnitude of the postoperative risk of venous thromboembolism in middle aged women: prospective cohort study. BMJ 2009;339:b4583