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Systematic Review

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 (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 surgery[12,13], 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[2]. TXA is inexpensive, costing €20 for a single dose[15], 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 review[19] 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[16] 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[20] reviewed only four[21–24] were in abdominal or pelvic surgery; the majority were studies in orthopaedic[25–43], cardiac[44], and head and neck surgery[45]. 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[46] 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.

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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.

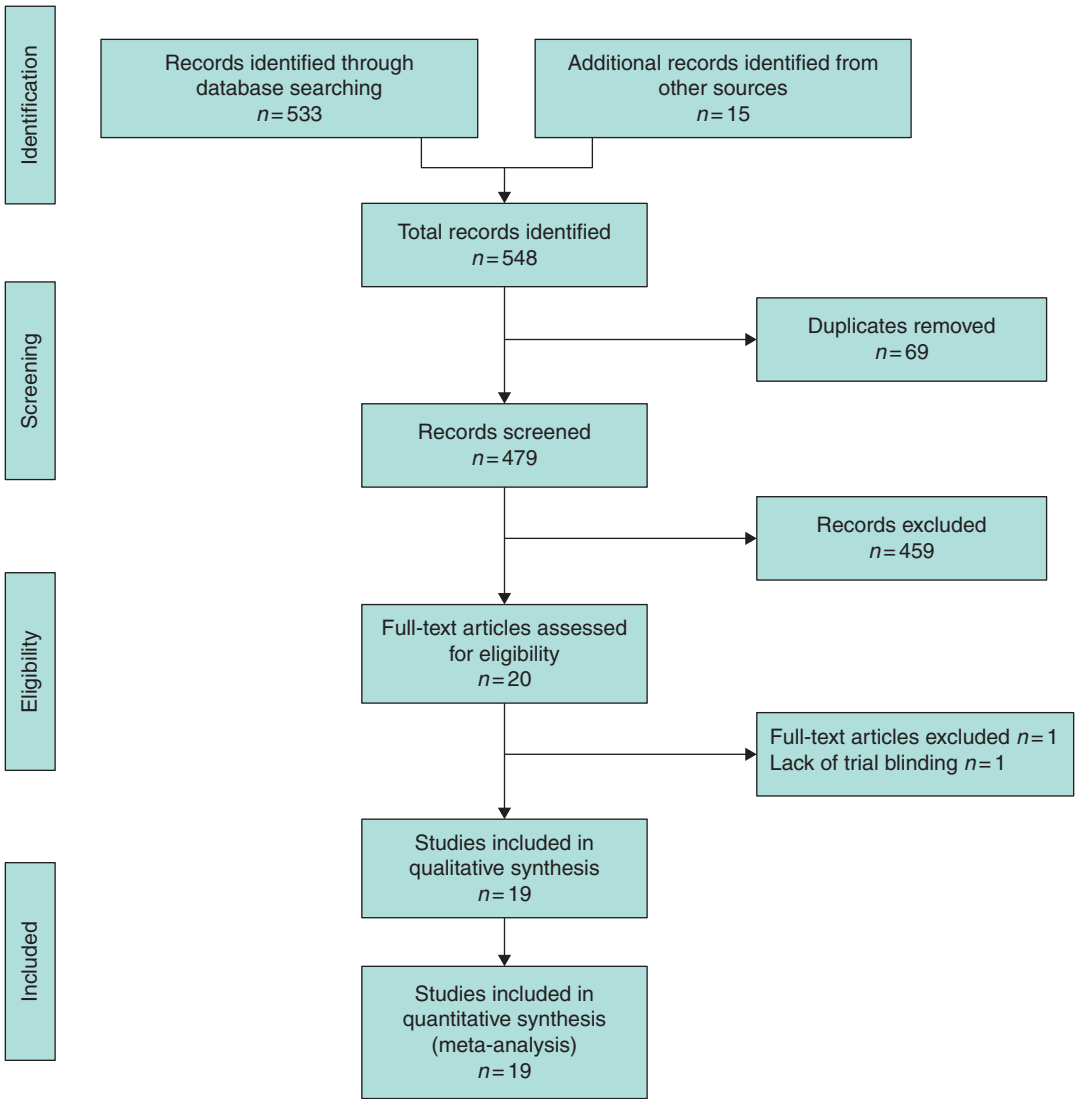

Fig. 1 PRISMA diagram showing selection of articles for review

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[47]. 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[47]. Publication bias was assessed as described by Eggers and colleagues[48], using visual inspection for asymmetry of the funnel plot based on the primary outcome.

Protocol registration

The protocol for this systematic review[49] 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[22], leaving 19 RCTs[50–68] 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)[50], urology

Table 1 Study characteristics

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 Abdominoperineal resection Hemicolectomy Uterine myomectomy Radical nephrectomy Radical cystectomy Hysterectomy Pancreatectomy Sigmoidectomy
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
Topsoee *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	Caesarean section
Pfizer[55]	2009–2011	India (single centre)	44	General surgery	Biliary tract surgical procedures Pancreatoduodenectomy Oesophagectomy Colectomy Gastrectomy
Crescenti *et al.*[52]	2008–2010	Italy (single centre)	200	Urology	Retropubic prostatectomy
Movafegh *et al.*[68]	2009–2010	Iran (single centre)	100	Obstetrics	Caesarian section
Caglar *et al.*[61]	2004	Turkey (single centre)	100	Gynaecology	Myomectomy

*The study recruited 129 patients; however only 86 were eligible for inclusion in this current analysis. ^AAA, abdominal aortic aneurysm.

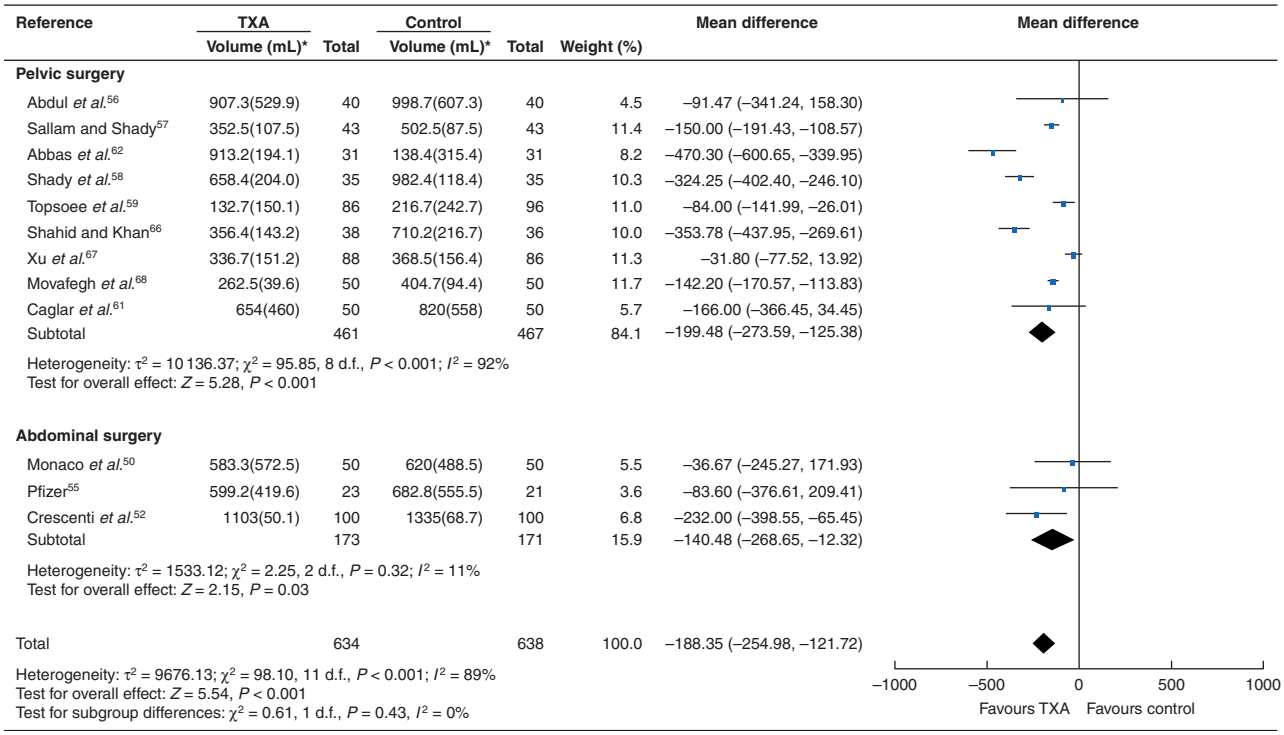

Fig. 2 Meta-analysis of the effect of tranexamic acid on intraoperative blood loss

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.

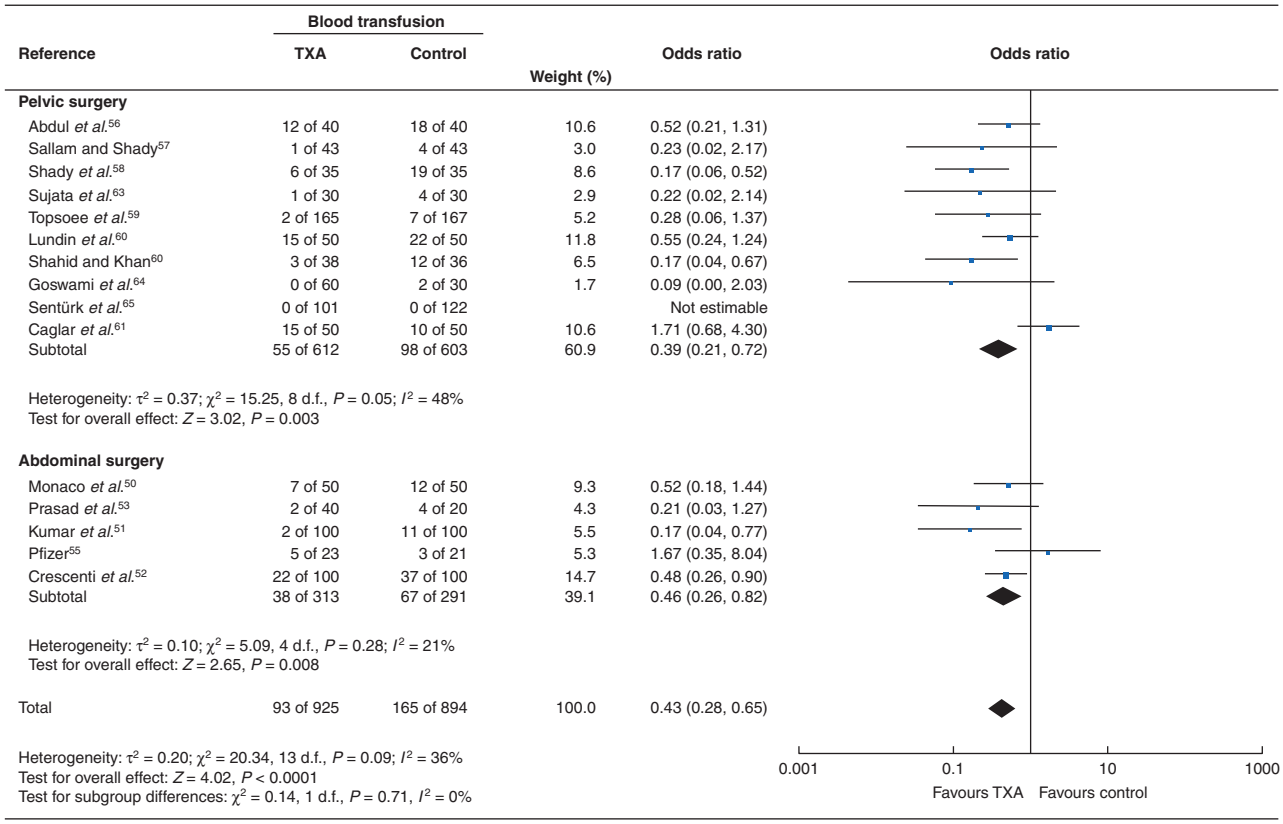

Fig. 3 Meta-analysis of the effect of tranexamic acid on the need for blood transfusion

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

Reference	TXA		Control			Mean difference
	Units*	Total	Units*	Total	Weight (%)	
Abdul *et al.*[56]	0.75(1.28)	40	1.13(1.64)	40	18.4	−0.38 (−1.02, 0.26)
Lundin *et al.*[60]	2.26(1.11)	50	2.35(1.34)	50	23.1	−0.09 (−0.57, 0.39)
Crescenti *et al.*[52]	0.35(0.75)	100	0.82(1.13)	100	29.7	−0.47 (−0.74, −0.20)
Caglar *et al.*[61]	0.54(0.89)	50	0.28(0.61)	50	28.8	0.26 (−0.04, 0.56)
Total		240		240	100.0	−0.16 (−0.56, 0.25)

Heterogeneity: $\tau^2 = 0.13$; $\chi^2 = 13.33$, 3 d.f., $P = 0.004$; $I^2 = 77\%$
Test for overall effect: $Z = 0.75$, $P = 0.45$

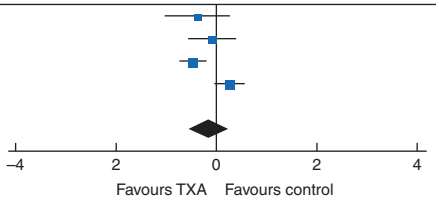

Fig. 4 Meta-analysis of the effect of tranexamic acid on units of blood transfused

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.

Reference	Thromboembolic events			Odds ratio
	TXA	Control	Weight (%)	
Monaco *et al.*[50]	0 of 50	0 of 50		Not estimable
Abdul *et al.*[56]	0 of 40	0 of 40		Not estimable
Sallam and Shady[57]	0 of 43	0 of 43		Not estimable
Prasad *et al.*[53]	0 of 40	0 of 20		Not estimable
Alhomoud[54]	0 of 25	0 of 25		Not estimable
Topsoee *et al.*[59]	0 of 165	0 of 167		Not estimable
Lundin *et al.*[60]	2 of 50	5 of 50	36.3	0.38 (0.07, 2.03)
Kumar *et al.*[51]	0 of 100	0 of 100		Not estimable
Sentürk *et al.*[65]	0 of 101	0 of 122		Not estimable
Shahid and Khan[66]	0 of 38	0 of 36		Not estimable
Goswami *et al.*[64]	0 of 60	0 of 30		Not estimable
Xu *et al.*[67]	2 of 88	2 of 86	26.3	0.98 (0.13, 7.09)
Pfizer[55]	0 of 23	0 of 21		Not estimable
Crescenti *et al.*[52]	2 of 100	5 of 100	37.4	0.39 (0.07, 2.05)
Caglar *et al.*[61]	0 of 50	0 of 50		Not estimable
Total	6 of 973	12 of 940	100.0	0.49 (0.18, 1.35)

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.64$, 2 d.f., $P = 0.73$; $I^2 = 0\%$
Test for overall effect: $Z = 1.38$, $P = 0.17$

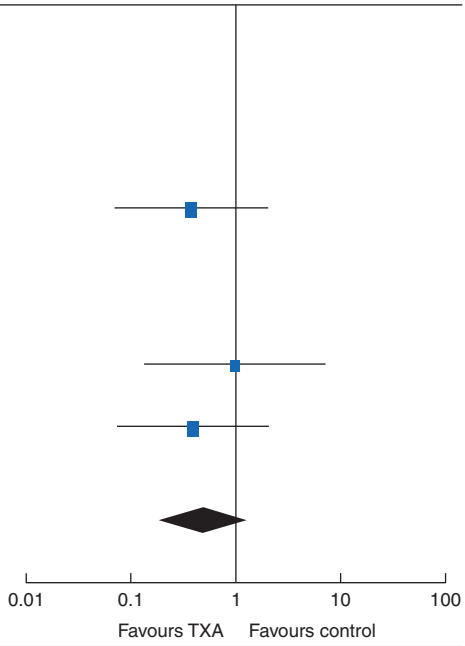

Fig. 5 Meta-analysis of the effect of tranexamic acid on thromboembolic events

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

(2)[51,52], general surgery (3)[53–55], gynaecology (6)[56–61], and obstetrics (7)[62–68].

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.

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 ($I^2 = 92$

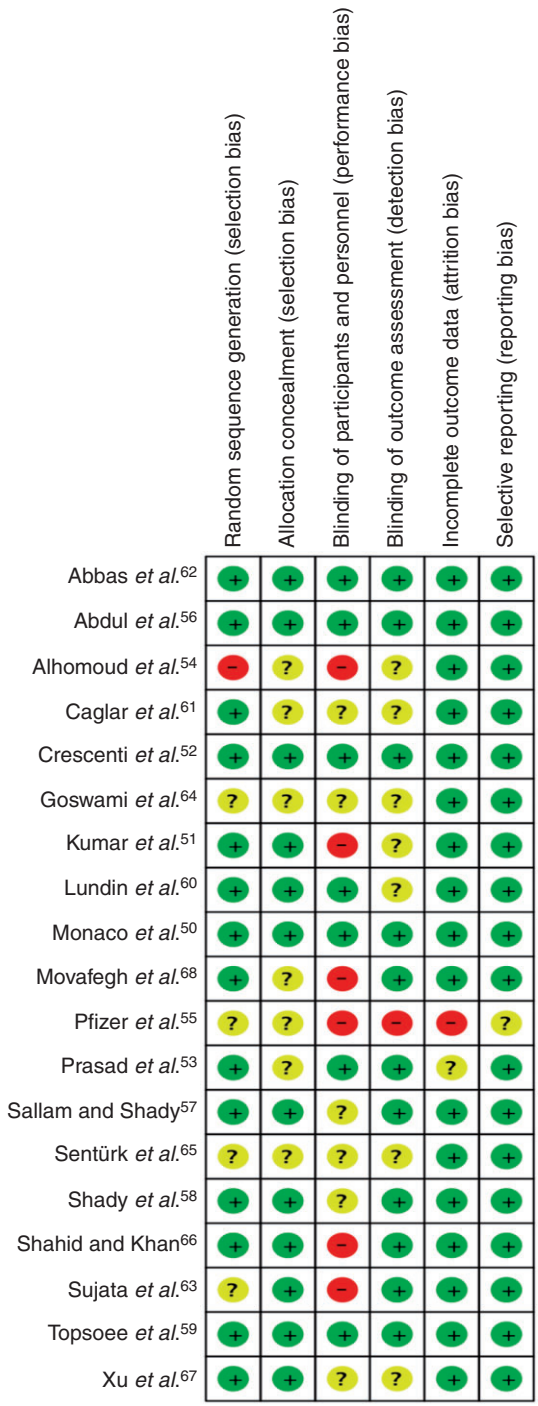

Fig. 6 Risk-of-bias summary: review authors' judgements about each risk-of-bias item for each included study

+, Low risk of bias; ?, unclear risk of bias; –, high risk of bias.

per cent), and was not resolved by further stratification into gynaecology and obstetrics.

Need for perioperative blood transfusion

Fifteen studies[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[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[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[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[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[11]. The multicentre WOMAN trial[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[5] 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[46] 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[10,11] and orthopaedic[25–43] 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[60] 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[46], 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[8] 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 (*Table S2*). The timing of administration of TXA ranged from 30 min before operation to the exact moment of knife to skin, and two studies[60,63] 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[56,60] relied on clinicians' subjective decision, whereas seven[51,57–59,64–66] did not describe a protocol for triggering transfusions, and only six[50,52,53,55,61,63] 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[60] reported asymptomatic VTEs. Follow-up limited to time of hospital discharge is known to capture thromboembolic events inadequately[70–72]. 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

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