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ORIGINAL RESEARCH ARTICLES

In adult patients presenting as emergencies with upper gastrointestinal bleeding, does tranexamic acid decrease mortality?

Chez les patients adultes se présentant en urgence avec des saignements gastro-intestinaux supérieurs, l'acide tranexamique fait-il diminuer la mortalité?

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Upper gastrointestinal bleeding (UGIB) is a common Emergency Centre presentation with a high mortality (5–30%). Despite theoretical benefits, tranexamic acid is not widely used for this condition. Tranexamic acid is widely available in the developing world and is on the World Health Organisation's essential medicines list. This review considers the following three-part question: "In adult patients with upper gastrointestinal bleeding, does tranexamic acid decrease mortality? A systematic review of the literature was performed (1900–2012). Databases searched included: MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, National Research Register, NIHR CRN portfolio, and http://ClinicalTrials.gov/. Grey literature databases searched included: Open Grey, Worldcat.org and Google Scholar. The conclusion of this review is that in adult patients with upper gastrointestinal bleeding, the administration of tranexamic acid may lead to a significant decrease in mortality.

Le saignement gastro-intestinal supérieur (SGIS) constitue une affection courante dans les centres d'urgence entraînant un taux de mortalité élevé (5–30%). Malgré les avantages théoriques, l'acide tranexamique n'est pas largement utilisé pour traiter cette affection. L'acide tranexamique est largement disponible dans le monde en développement et figure sur la liste des médicaments essentiels de l'Organisation mondiale de la Santé. Cette étude se penche sur la question suivante à trois volets: « Chez les patients adultes souffrant de saignements gastro-intestinaux supérieurs, l'acide tranexamique fait-il diminuer la mortalité ? » Une étude systématique de la littérature a été réalisée (1900–2012). Les bases de données consultées ont notamment été les suivantes: MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, National Research Register, NIHR CRN Portfolio et http://ClinicalTrials.gov/. Les bases de données consultées dans la documentation non officielle (littérature « grise ») ont notamment été les suivantes: Open Grey, Worldcat.org et Google Scholar. La conclusion de cette étude est que chez les patients adultes souffrant de saignements gastro-intestinaux supérieurs, l'administration d'acide tranexamique peut conduire à une diminution significative de la mortalité.

African relevance

- Tranexamic acid is widely available throughout Africa.
- Tranexamic acid is likely to reduce mortality in upper gastrointestinal bleeding.
- An initial dose of 1 g IV should be given followed by 1 g TDS/QDS.

Introduction

Upper gastrointestinal bleed (UGIB) is a relatively common medical presentation worldwide, accounting for a significant number of emergency centre (EC) visits.[1] Despite having a high mortality (5–30%[2]), evidence-based medical treatment options for this condition remain sparse.

In the past thirty years, medical treatment for UGIB has centred on proton pump inhibitor therapy and, in selected cases, somatostatin analogues. Recent Cochrane reviews do not support the routine use of either of these therapies.[3,4]

Tranexamic acid (TXA) is a widely available antifibrinolytic medication that has been used clinically in various settings, including resource poor environments, since its development in the 1960s. It is most commonly used in the context of both severe bleeding and predicted severe bleeding (e.g., surgical intervention).[5] It is currently not commonly used in the management of UGIB.[2,6]

UGIB is defined as bleeding originating from a source proximal to the ligament of Treitz: the duodenojejunal junction. Causes of major UGIB bleeding can be found in Table 1.

The challenge of obtaining rapid haemostasis in those with UGIB is multifactorial. Patient related factors include propensity to bleed without clot formation (e.g., those on warfarin) and those with inherent clotting abnormalities (e.g., alcohol related liver disease).

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Table 1 Causes of major UGIB.

Peptic ulcer disease (30–50%)[6]
Oesophageal and gastric varices
Haemorrhagic gastritis
Oesophagitis
Duodenitis
Mallory-Weiss tear
Angiodysplasia
Upper gastrointestinal malignancy
Anastomotic ulcers (after PUD surgery or bariatric surgery)
Dieulafoy lesion

Note: PUD = peptic ulcer disease.
Adapted from: Ref. [1].

The gastric and duodenal environment is hostile to clot formation. Clot formation is impaired by:

- Direct effect of the acidic environment impairing platelet aggregation and clot formation.[7]
- Acceleration of clot lysis by gastric juice. This fibrinolytic effect is likely to be mediated both by pepsin and other unknown acid dependent proteases.[8,9]
- Gastrointestinal mobility during haemorrhage.[10]
- Marked vascularity with the absence of autoregulation of local blood flow.[8]

TXA is a plasminogen inhibitor. Plasminogen is a precursor to plasmin, a key enzyme in fibrinolysis. In addition, TXA has a direct effect on reducing the fibrinolytic activity of pepsin independent of pH. It is postulated that TXA also has a significant effect on other proteases that cause clot destruction.[8,9,11–15]

More recently, TXA has been identified as having anti-inflammatory effects. This is achieved by binding to cells involved in the inflammation process including macrophages, neutrophils, etc., as well as inhibiting the pro-inflammatory effects of plasminogen.[16]

Objective

The objective of this review is demonstrated using a three-part question: In [adult patients presenting as an emergency with upper gastrointestinal bleeding] does [tranexamic acid] decrease [mortality]?

Various surrogate markers are used throughout this literature base. Mortality is a definitive patient centred outcome, which has clear diagnostic criteria and is not subject to the bias of other measures such as rebleeding or transfusion requirements.[17,18]

Literature search methodology

A literature search was conducted for all journal article types, including but not limited to: basic science, *in vitro* studies, guidelines, clinical and preclinical trials of all designs, (systematic) reviews, and meta-analyses on the use of TXA in UGIB. Search dates were from January 1900 through October 2012. Various combinations of searches were carried out. Upper gastrointestinal bleeding is subject to varied terminology within the literature. Narrower search strategies attempting to identify this specific bleeding subset were deemed unsuccessful and the search terms were ultimately rejected. The final search terms were Tranexamic Acid AND (bleed$ or haemorrhage). By starting with a wide comprehensive search strategy, the effect of synonyms, related terms, and variant spellings was minimised whilst simultaneously decreasing the likelihood of missing relevant publications. This search strategy was adapted and applied to MEDLINE (using the PubMed Interface), EMBASE (via NHS Athens), Cochrane Central Register of Controlled Trials, National Research Register (NRR), NIHR CRN portfolio, and http://ClinicalTrials.gov/. Grey literature databases were also searched and included Open Grey, Worldcat.org, and Google Scholar. All searches were confined to the English language. A manual review of abstracts when available, and otherwise the full texts, was performed with items relevant to the objective included for second review. On second review, full texts were reviewed and those relevant to the objective included. A final review of reference lists from relevant articles was carried out and articles relevant to the objective were also included for final review (Fig. 1).

Review of the literature

Lab and animal studies

A small number of *in vitro* and animal studies report the various stages of gastric clot formation, subsequent fibrinolysis and the effect TXA has upon these processes.[8,9,11–15] All of the studies report a relationship between TXA and improved clot formation and maintenance.

Case series

Two case series' with 98 and 159 consecutive patients were all treated with TXA and conventional therapy.[19,20] The authors report a lower than expected mortality rate of 4.1% and 4.5%, respectively, and conclude that their treatment protocol was successful.

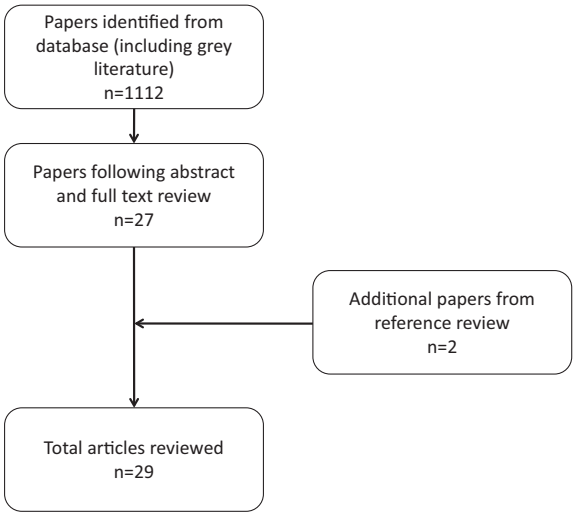

Figure 1 Flow diagram of process of systematic literature search.

Cohort studies

Sabovic et al. report a series of 20 consecutive renal dialysis patients with a total of 36 episodes of UGIB.[21] Physicians chose whether to administer TXA or not (a clear source of bias); additionally no blinding occurred and no placebo was used. The authors reported a statistically significant ($p < 0.05$) reduction in: early rebleeding, early and late rebleeding, repeated endoscopic procedure, and the number of blood transfusions required.

Randomised controlled trials

Seven randomised controlled trials (RCT) were identified that were relevant to the study question.

1. *Cormack et al. (1973): Tranexamic acid in upper gastrointestinal haemorrhage*

The first of these trials was published in 1973.[22] Cormack et al. report a RCT of 150 consecutive patients carried out between 1969 and 1971 at a single centre (UK). They include all patients presenting with frank haematemesis or melaena but lack clarity in their exclusion criteria: ''those with conditions known to be fatal''. The authors do not describe their methods of randomisation or the extent of their blinding (described as double blind). The intervention was oral TXA 1.5 g 8hrly or placebo tablets. A composite endpoint was used: ''treatment failure'' which included death, need for surgery, and rebleeding. Seventy-six patients received TXA and 74 placebo. The groups were well matched in terms of age, sex, and severity of symptoms. Intention to treat analysis was carried out for primary endpoint. When the composite primary endpoint of treatment failure was considered, a non-significant difference was reported: 15 patients failed treatment in the TXA group and 20 in the placebo group. The authors go on to describe an unplanned subgroup analysis (excluding patients with hiatus hernia or oesophageal varices – a barium meal was carried out on survivors) in which they report a statistically significant ($p < 0.05$) outcome between the groups in favour of TXA in relation to treatment failure. This is a clear example of survivor bias.

The authors recruit a further ten patients at the end of the study to test oral absorption of TXA. They report that it is well absorbed via the oral route despite concurrent UGIB.

Author's final discussion recommends TXA for bleeding distal to the gastroesophageal junction – to be confirmed by gastroscopy prior to initiation of treatment. The authors report that the trial was industry sponsored.

2. *Engqvist et al. (1979): Tranexamic acid in massive haemorrhage from the upper gastrointestinal tract: a double blind study*

This study was published in 1979, four years after study's completion.[23] This single-centre study (Stockholm) of intensive care patients was conducted over 15 months: 1974–5. Patients required a history of haematemesis and/or melaena with defined measurable signs of circulatory 'embarrassment' to be included in the trial. Patients were excluded with either a history of thromboembolism or renal disease. It is not clear if consecutive patients were recruited or assessed for eligibility. Restricted randomisation was used to ensure equal distribution of males and females. Patients received either TXA in intensive care at 1 g 4hrly IV (maximum three days) and then on ward 1.5 g 6hrly (maximum four days) or an equivalent IV or oral placebo. Primary or secondary endpoints are not defined in the methodology.

Of 204 patients entering the study, many (55) were excluded on the basis of only minor bleeding or having not received therapy according to the protocol. Intention to treat analysis was not performed. Of patients analysed, 76 received TXA and 73 placebo. The investigators found a lower rate of continued bleeding, operations, and deaths in the TXA group; none of these achieved statistical significance.

3. *Biggs et al. (1976): Tranexamic acid and upper gastrointestinal haemorrhage – a double blind trial*

This single centre Australian study recruited consecutive patients presenting to the EC with confirmed symptoms of UGIB – a witnessed episode or positive gastric aspirate.[24] Patients not admitted to the hospital, those who were pregnant, had chronic renal impairment, vascular surgery, or a thromboembolic event in the preceding 12 months were excluded. Patients were randomised to receive 1 g IV and 1 g PO 8hrly for 48 h followed by 1 g PO 8hrly for a further 72 h or an equivalent placebo. The trial was conducted in a double blind fashion. The authors do not name their primary endpoints but recorded transfusion requirements, requirement for surgery and mortality. Two hundred patients (unpowered) were recruited; 103 received treatment and 97 placebo. The authors found no statistical significance in transfusion requirements or mortality (two died in TXA group, four in placebo group). They did find statistically less operative intervention required in the treatment group (seven in TXA group, 21 in placebo group). This trial was industry sponsored.

4. *Berqvist et al. (1980): Local inhibition of the fibrinolytic system in patients with massive upper gastrointestinal hemorrhage.*[25]

This unpowered, single centre trial recruited 50 patients with haematemesis and/or melaena that had signs of circulatory compromise (undefined). Patients were randomised to receive NG placebo or TXA 2 g 4hrly for 48 h. The trial was conducted in a double blind manner. Following exclusions on the basis of incorrectly enrolled patients and concurrent therapies, 22 patients remained in the placebo group and 21 in the treated group; intention to treat analysis was not performed. The trial found no difference in operative frequency but a large difference in mortality: placebo 22.7%, and TXA 12.3%, however p-values were not reported.

5. *Barer et al. (1983): Cimetidine and tranexamic acid in the treatment of acute upper-gastrointestinal-tract bleeding.*[26]

This study was conducted across two hospitals in the UK from January 1980–1982. All patients admitted via EC with a primary diagnosis of haematemesis and/or melaena were considered for eligibility. Patients with bleeding requiring immediate operative intervention, other ''serious medical conditions'' that primarily affected management, and in those

where the bleeding was not considered serious were excluded. Patients were randomised in blocks of six to receive a treatment pack containing cimetidine (40 g IV 6hrly for 48 h, followed by 400 mg PO 6hrly for 5 days), TXA (1 g IV 6hrly for 48 h followed by 1 g PO 6hrly for 5 days) or an identically appearing placebo to the same schedule. The study was powered with an 85% chance of detecting a significant ($p < 0.05$) halving of either rebleeding or death in either group (750 patients). Seven hundred and seventy-five patients were recruited across the three groups (achieved power). On intention to treat analysis, no difference was found in regard to rebleeding and operation rates. However, both TXA and cimetidine achieved a statistically significant decrease in mortality with an actual risk reduction (ARR) of 7.2% and 5.7% respectively when compared to placebo. For TXA, this is a relative risk reduction (RRR) of >50%.

6. *Von Holstein et al. (1987): Tranexamic acid as an aid to reducing blood transfusion requirements in gastric and duodenal bleeding.*[27]

This single centre study recruited all patients presenting with suspected UGIB to a Swedish hospital. Patients were excluded if they had thromboembolic disease, bleeding or coagulation defects, were taking anticoagulants, or were pregnant. Patients were randomised in blocks of ten to receive TXA or placebo IV 1 g every 4hrly for 3 days followed by 1.5 g PO 6hrly for a further 3 days. After allocation, patients were examined endoscopically. Those with evidence of cancer, an oesophageal source of bleeding, or no clear source of bleeding were excluded. Additionally, patients with evidence of renal failure were also excluded. Intention to treat was not performed. Blood was transfused to a pre-established guideline but indications for surgery were softer. The study was powered for a primary outcome of "blood loss" (150 patients). One hundred and fifty-four of a total of 328 recruited patients were included for final analysis (achieved power). The trial found statistically significant differences for blood transfusions (2.2 vs 3.2 units $p = 0.018$) and operation rates ($p = 0.010$). More patients in the placebo group rebled (19 vs 10) and died (4 vs 2), however, neither of these achieved statistical significance.

7. *Hawkey et al. (2001): Drug Treatments in upper gastrointestinal bleeding: value of endoscopic findings as surrogate end points.*[18]

This trial takes a different approach to those previously discussed. The first of two aims was to develop a measure to reflect bleeding severity and subsequent clinically important end points. The second was to assess the effect of oral medications (TXA and a PPI) on this end point. Four hundred and fourteen (powered to 400) consecutive patients with suspected UGIB were enrolled in this two-centre study (UK). Those requiring immediate surgery, with conditions making active treatment inappropriate (e.g., malignancy), pregnancy, lactation, active thromboembolism, coagulopathy, renal failure, or on phenytoin were excluded. Patients were block randomised to receive TXA (PO 2 g followed by 1 g QDS), Lansoprazole (60 mg PO followed by 30 mg QDS), both regimes combined, or placebo. A double dummy technique was used to maintain blinding. Patients were endoscoped with adrenaline therapy and given an endoscopic assessment score. Multiple clinical outcome analysis and complex multi-regression were used to draw conclusions. The authors conclude that the presence of blood in the stomach reflected subsequent clinical risk and therefore TXA, Lansoprazole, and a combination of the two without synergism reduced this blood.

Reviews and systematic reviews

A number of reviews of varying quality were identified in the literature search. Seven reviewed a range of drug treatments for UGIB[6,28–35], two papers review the efficacy of TXA/antifibrinolytics in a variety of clinical settings[31,34]) and one focused on TXA in UGIB.[36] The majority of reviews presented the use of TXA in UGIB in a positive context, with the exception of those carried out by North American authors.[6,28,30,35]

Meta-analyses

The literature search identified two meta-analyses, the first performed by Henry and O'Connell in 1989.[37] After an appropriate literature search, this well thought out study

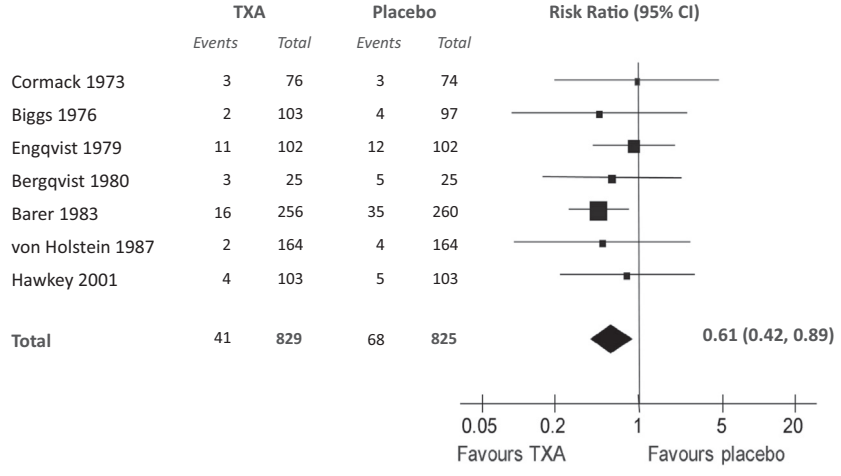

Figure 2 Forest plot of randomised controlled trial risk ratios of tranexamic acid vs placebo.

Table 2 Summary of randomised controlled trials.

Author year	Centre	Patients	Exclusions	Intervention	Outcome	Included	Results	Side effects
Cormack et al. (1973)	Single, UK	Admitted patients: all haematemesis or melaena	Unclear: "Conditions known to be fatal"	Oral TXA, 1.5 g 8hrly	Composite: death, need for surgery, rebleeding	150	No difference for primary endpoints	1 Patient had nausea and vomiting (TXA)
Engvist et al. (1979)	Single, Sweden	ICU patients with haematemesis and/or melaena with "circulatory embarrassment"	History of thrombo-embolism or defined renal failure	IV TXA, 1 g 4hrly for 3 days, then PO 1.5 g QDS for 4 days	Unclear but included death, need for surgery and rebleeding	149	Trend towards less deaths, need for surgery and rebleeding in intervention group (non-significant)	4 Thrombo-embolic episodes in TXA group, 2 in placebo
Biggs et al. (1976)	Single, Australia	ED patients: witnessed haematemesis or positive gastric aspirate	Not admitted, pregnant, CRF, history of thrombo-embolism, vascular surgery	Oral and IV TXA, 1 g 8hrly for 2 days, then PO 1 g 8hrly for 3 days	Unclear but included death, need for surgery and transfusion requirements	200	No difference in mortality, transfusion requirements. Less operative intervention in intervention group (statistically significant)	None major. Minor similar between groups.
Bergqvist et al. (1980)	Single, Sweden	Unclear population: with haematemesis and/or melaena with undefined shock	Not stated	NG TXA, 2 g 4hrly for 2 days	Requirement for and day of operation, death and day of death	43	Decrease in mortality in intervention group (p-value not reported)	Not discussed
Barer et al. (1983)	Two, UK	Admitted with primary diagnosis of haematemesis or melaena	Immediate operative intervention, "serious medical conditions", not serious bleeding	IV TXA, 1 g 6hrly for 2 days, then PO 1 g QDS for 5 days	Death, need for surgery and rebleeding	775	Statistically significant decrease in mortality	1 Thrombo-embolic episode in patient with polycythemia (TXA group)
Von Holstein et al. (1987)	Single, Sweden	Admitted patients with suspicion of UGIB	Thrombo-embolic disease, bleeding or coagulation defect or on anticoagulants	IV TXA, 1 g 4hrly for 3 days, then PO 1 g QDS for 3 days	Transfusion requirements, need for surgery, rebleeding and death	154	Statistically significant decrease in transfusion requirement and need for surgery	2 Episodes of thrombo-phlebitis and 1 thrombo-embolic episode (TXA group)
Hawkey et al. (2001)	Two, UK	Admitted patients with suspicion of UGIB	Immediate operative intervention, pregnant, lactating, defined renal failure, coagulopathic, on phenytoin	PO TXA 2 g followed by 1 g QDS	Blood in stomach as predictor of clinical risk	414	Statistically significant decrease in blood in the stomach for TXA	No difference between groups

identified the first six RCTs discussed above as suitable for inclusion.[22,23,25–27] They identified and overcame the failure of some of the authors to carry out intention to treat analysis by contacting the authors directly and successfully obtaining the data of excluded patients in all but one trial. The authors combined 1267 patients for analysis. Unable to accurately assess the heterogeneity of the data, the authors carried out a method of Peto and method of DerSimonian and Laird analysis of outcomes. Using both methods they found a highly statistically significant reduction in mortality ($p = 0.01$ and 0.02) with an estimated effect of a 40% decrease in mortality. Data for rebleeding and need for operative intervention were more heterogenous as would be expected for a 'softer' outcome more prone to physician bias, but achieved an estimated effect of a 20–30% decrease in rebleeding and a 30–40% reduction in operation rate. The authors appropriately discussed the various bias this meta-analysis may be subject to and correctly identified their inability to account for publication bias.

Gluud et al. took a non-narrative approach to their systematic review and meta-analysis which included all seven of the RCTs discussed above.[38] They performed a ''worse case scenario'' statistical analysis and found potentially no difference in mortality between intervention and placebo. They did not use the additional data available from Henry's meta-analysis in their calculations. The authors concluded that TXA may reduce mortality and had a limited side effect profile (Fig. 2). Despite this, they could not recommend its use until more evidence was available. This review formed the basis of the author's subsequent Cochrane review.[39]

Discussion

Principal findings

The principal findings for the RCTs are summarised in Table 2. In short:

- The laboratory and animal based studies present a strong experimental base for benefit from TXA.
- The two case studies and single cohort study reveal the potential benefit of TXA administration in humans.
- A majority of the RCTs show a statistically significant benefit in at least one of their outcomes (Table 3).
- None of the RCTs or meta-analyses showed evidence of harm, however, they were not powered to do this.
- Both meta-analyses provide convincing evidence of a decrease in a solid patient centred outcome, namely, a 40% decrease in mortality.

Strengths and weaknesses

The RCTs suffer from a number of common failings that limit their ability to unequivocally answer the clinical question. Common strengths and weaknesses of the RCTs are summarised in Table 4.

The quality of trial designs shows improvement over time. A general increase in quality of trials over a similar time period has been supported by an increasing focus on evidence-based medicine, an increased awareness of trial design, and the production of respected guidelines.[40]

A common problem across the literature is the use of ''soft'' endpoints. Unless blood transfusions and operative interventions are initiated by comprehensive predefined indications there is a significant potential for physician- introduced bias. Henry's meta-analysis identified heterogeneity in the operative requirement outcome.[37] The use of ''harder'' endpoints such as in-hospital mortality though ideal, in the context of UGIB, requires recruitment of a larger sample size.

External validity and applicability

Though small differences in definitions exist between external validity and applicability, the concept of ''generalisability'' encompasses both.

Many similarities exist between the personnel used in the trials and our target patients. Significant improvements in the outcome of patients with UGIB have not occurred in the last 30 years.[28] Wide inclusion criteria and few exclusion criteria, though occasionally poorly described, further enhance this evidence base's external validity. The most significant threats to these trials' external validity are the questions over their internal validity.

Validity in a resource poor environment

The aetiology of UGIB is similar in European and resource poor populations. TXA is a cheap, readily available drug, widely used in resource poor areas. TXA is easily prepared and administered intravenously, without the need for intensive or specialist monitoring. The HALT-IT trial is currently recruiting patients in a resource poor and developed world setting. This multi-centre pragmatic, randomised, double blind, placebo-controlled trial aims to recruit 8,000 patients with significant lower and upper gastrointestinal bleeding. The pragmatic nature of this trial and the potential for sub-group analysis could 'prove' validity in the resource poor environment.

Table 3 Summary of outcomes from randomised controlled trials.

Author	Mortality	Rebleeding	Transfusion	Operation	Other
Cormack et al.	No difference	No difference	NA	No difference	NA
Engvist et al.	Trend decrease	Trend decrease	NA	Trend decrease	NA
Biggs et al.	No difference	NA	No difference	Decrease	NA
Bergqvist et al.	Decrease	NA	NA	No difference	NA
Barer et al.	Decrease	No difference	No difference	No difference	NA
Von Holstein et al.	No difference	Trend decrease	Decrease	Decrease	NA
Hawkey et al.	No difference	No difference	No difference	No difference	Decreased blood in stomach

Table 4 Summary of strengths and weaknesses of randomised controlled trials.

Author	Population selection	Consecutive patients	Endpoints	Powered	Randomisation type	Double blinding	Intention to treat	Industry sponsored
Cormack et al.	Unclear exclusions	Yes	Composite	No	Not described	Not described	Yes	Yes
Engvist et al.	Unclear inclusions	Unclear	Unclear	No	Block	Not described	No	Not stated
Biggs et al.	Clear	Yes	Unclear	No	Not described	Not described	Yes	Yes
Bergqvist et al.	Unclear inclusions and exclusions	Unclear	Clear	No	Not described	Not described	No	Not stated
Barer et al.	Clear	Yes	Clear	Yes	Block	Partially described	Yes	Yes
Von Holstein et al.	Clear	Yes	Clear	Yes	Block	Partially described	No	Yes
Hawkey et al.	Clear	Yes	Determined	Yes	Block	Partially described	No	Yes

Conclusion

It is likely that in adult patients with upper gastrointestinal bleeding, the administration of tranexamic acid decreases mortality. The HALT-IT trial should definitively answer this question in the near future.

Conflict of interest

The author declare no conflict of interest.

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