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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.

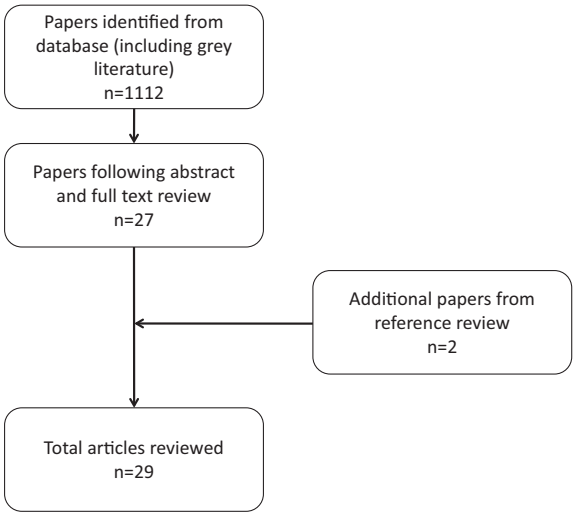

Figure 1 Flow diagram of process of systematic literature search.