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How effective is tranexamic acid for acute gastrointestinal bleeding?

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This is one of a series of occasional articles that highlight areas of practice where management lacks convincing supporting evidence. The series adviser is David Tovey, editor in chief, the Cochrane Library. To suggest a topic for this series, please email us at uncertainties@bmj.com.

Acute gastrointestinal bleeding is a common emergency. It encompasses upper gastrointestinal bleeding (such as from peptic ulcers and oesophageal varices) and lower gastrointestinal bleeding (commonly from diverticular disease, colitis, and cancer). The risk is greater in older adults, and many cases are associated with the use of non-steroidal anti-inflammatory drugs.

In the UK acute gastrointestinal bleeding accounts for about 75 000 hospital admissions each year and has a case fatality of about 10%. Case fatality may be higher in patients already hospitalised for another condition. More effective treatments for acute gastrointestinal bleeding are needed.

Tranexamic acid (TXA) reduces clot breakdown by inhibiting the action of plasmin, which is involved in fibrinolysis. A systematic review of randomised controlled trials in surgical patients shows that TXA, given before or during surgery, reduces the probability of receiving a blood transfusion by about 10% (95% confidence interval 0.85 to 0.96). The effect of tranexamic acid on thromboembolic events such as myocardial infarction, stroke, deep vein thrombosis, and pulmonary embolism, however, was uncertain.

The CRASH-2 trial showed that administration of TXA to bleeding trauma patients reduced death due to bleeding (relative risk 0.62, 95% confidence interval 0.58 to 0.65). The effect of tranexamic acid on thromboembolic events such as myocardial infarction, stroke, deep vein thrombosis, and pulmonary embolism, however, was uncertain.

The knowledge that TXA reduces bleeding in surgery and reduces mortality in trauma raises the possibility that it might also be effective in gastrointestinal bleeding. Fibrinolysis may play a role in gastrointestinal bleeding because of premature breakdown of fibrin blood clots at the bleeding site. Many patients with acute upper gastrointestinal bleeding have elevated levels of fibrin degradation products (a marker of fibrinolysis), and these patients have worse outcomes.

What is the evidence of the uncertainty?

Through searches of PubMed, Embase, and the Cochrane Central Database of Controlled Trials, we identified nine randomised comparisons from eight clinical trials of the use of TXA in upper gastrointestinal bleeding and none in lower gastrointestinal bleeding (figure). Seven of the identified trials were also included in a Cochrane systematic review on the effectiveness of TXA in upper gastrointestinal bleeding. The pooled result shows a statistically significant reduction in the risk of death in patients receiving TXA (relative risk 0.66, 0.47 to 0.93) (figure). However, the quality of the trials was poor. Only one trial had adequate allocation concealment. In several trials, patients were excluded after randomisation, and information on their outcomes was not reported, raising the possibility of selection bias. All but two trials were conducted before the widespread use of therapeutic endoscopy and proton pump inhibitors. Therefore, their results might not be applicable to current patients with gastrointestinal bleeding.

We conducted a trial sequential analysis to assess the reliability of the result from our systematic review and meta-analysis. This showed that about 5500 patients would need to have been included in clinical trials (many more than the current total) to have enough power to detect a plausible treatment effect. Thus, although the meta-analysis result is statistically significant (P<0.05), this could easily be a false positive result.

Only three trials reported data on adverse events. These studies were already included in the previous Cochrane review. The risk of thromboembolic events is about 1% overall and seemed to be higher in TXA treated patients (relative risk 1.86, 0.66 to 5.24). However, the result is imprecise and compatible with the play of chance.

Given these uncertainties, TXA is not routinely used or recommended for gastrointestinal bleeding. In a UK audit in 2007, fewer than 1% of patients with upper gastrointestinal bleeding received TXA. TXA is not referred to in two

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international consensus documents on the management of upper gastrointestinal bleeding, nor in the 2012 UK National Institute for Health and Care Excellence (NICE) guidelines for acute upper gastrointestinal bleeding.

Is ongoing research likely to provide relevant evidence?

Searches of the ClinicalTrials.gov trial registry suggest that there are two ongoing double blind randomised controlled trials of the use of intravenous TXA in gastrointestinal bleeding (described in the table⇓). In both trials, TXA or placebo is given in addition to the usual management of gastrointestinal bleeding. The TAUGIB trial includes patients with acute upper gastrointestinal bleeding before undergoing endoscopy, but it will not be large enough to determine reliably the effect of TXA on mortality and thromboembolic events. Assuming a mortality of 10% in the placebo group, a trial of 400 patients has only 10% power to detect a 25% reduction in mortality (10% to 7.5%).

The HALT-IT trial aims to recruit 8000 patients with acute gastrointestinal bleeding (upper or lower) and will have 90% power to detect a 25% reduction from 10% to 7.5% in mortality.

What should we do in the light of the uncertainty?

TXA is not routinely recommended for upper or lower gastrointestinal bleeding, and there are important uncertainties about its safety and effectiveness for this indication. Uncertainty about its effect on thromboembolic events is important, as many patients with acute gastrointestinal bleeding are older and have a high baseline risk of thromboembolism. In a UK survey, the median age of patients with gastrointestinal bleeding was 68 years, with about 18% having a history of ischaemic heart disease and 8% with a previous stroke. Clinicians have to decide whether to use TXA without reliable evidence of the balance between risk and benefit. However, in the context of such uncertainty the most appropriate management would be to include them in a randomised controlled trial. This will ensure that the uncertainty is resolved in a timely and scientifically defensible way.

In the meantime, current NICE guidelines suggest the following key points in the management of patients with upper gastrointestinal bleeding:

- Risk assessment, with Blatchford scoring system at first assessment and the full Rockall scoring system after endoscopy
- Fluid resuscitation
- Localisation of the bleeding site
- Therapeutic interventions to stop bleeding, including endoscopic treatment
- Prevention of re-bleeding

NICE guidelines are useful for standardising the management of acute upper gastrointestinal bleeding. However, the evidence base for some of the recommendations is weak. In addition, no recent guidelines are available for lower gastrointestinal bleeding. High quality research is needed to inform clinical decisions in the management of both upper and lower gastrointestinal bleeding.

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Table

<table>
<thead>
<tr>
<th>Trial (type)</th>
<th>Status</th>
<th>Population</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Primary outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAUGIB (double blind, randomised trial)</td>
<td>Currently recruiting</td>
<td>414 patients with upper GI bleeding before endoscopy</td>
<td>1 g IV bolus over 10 minutes followed by 1 g slow infusion over 8 hours</td>
<td>Placebo</td>
<td>Proportion of patients requiring early endoscopic treatment</td>
</tr>
<tr>
<td>HALT-IT (double blind, randomised trial)</td>
<td>Currently recruiting</td>
<td>8000 patients with significant acute GI bleeding</td>
<td>1 g IV bolus over 10 minutes followed by 3 g slow infusion over 24 hours</td>
<td>Placebo</td>
<td>Mortality in hospital within 28 days of randomisation</td>
</tr>
</tbody>
</table>

GI = gastrointestinal. IV = intravenous.
Meta-analysis and risk of bias summary of trials assessing effect of tranexamic acid (TXA) on death in acute gastrointestinal bleeding. All trials compared TXA with placebo unless stated otherwise.

<table>
<thead>
<tr>
<th>Trial</th>
<th>TXA (n/N)</th>
<th>Control (n/N)</th>
<th>Risk ratio (95% CI)*</th>
<th>Risk ratio (95% CI)*</th>
<th>Risk of bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bagrenko 2011</td>
<td>1/22</td>
<td>3/25</td>
<td>0.38 (0.04 to 3.38)</td>
<td>0.38 (0.04 to 3.38)</td>
<td>3</td>
</tr>
<tr>
<td>Barer 1993</td>
<td>16/256</td>
<td>35/260</td>
<td>0.46 (0.26 to 0.82)</td>
<td>0.46 (0.26 to 0.82)</td>
<td>3</td>
</tr>
<tr>
<td>Bergqvist 1980</td>
<td>3/21</td>
<td>5/22</td>
<td>0.63 (0.17 to 2.31)</td>
<td>0.63 (0.17 to 2.31)</td>
<td>3</td>
</tr>
<tr>
<td>Biggs 1976</td>
<td>2/103</td>
<td>4/97</td>
<td>0.47 (0.09 to 2.51)</td>
<td>0.47 (0.09 to 2.51)</td>
<td>3</td>
</tr>
<tr>
<td>Cormack 1973</td>
<td>3/76</td>
<td>3/74</td>
<td>0.97 (0.20 to 4.67)</td>
<td>0.97 (0.20 to 4.67)</td>
<td>3</td>
</tr>
<tr>
<td>Engqvist 1979</td>
<td>11/76</td>
<td>12/73</td>
<td>0.88 (0.41 to 1.87)</td>
<td>0.88 (0.41 to 1.87)</td>
<td>3</td>
</tr>
<tr>
<td>Hawkey 2001</td>
<td>3/103</td>
<td>5/103</td>
<td>0.80 (0.22 to 2.89)</td>
<td>0.80 (0.22 to 2.89)</td>
<td>3</td>
</tr>
<tr>
<td>Hawkey 2001b</td>
<td>5/106</td>
<td>2/102</td>
<td>2.41 (0.48 to 12.12)</td>
<td>2.41 (0.48 to 12.12)</td>
<td>3</td>
</tr>
<tr>
<td>Von Holstein 1983</td>
<td>4/94</td>
<td>6/108</td>
<td>0.77 (0.22 to 2.63)</td>
<td>0.77 (0.22 to 2.63)</td>
<td>3</td>
</tr>
<tr>
<td>Pooled: z²=5.29, P=0.02</td>
<td></td>
<td></td>
<td>0.66 (0.47 to 0.93)</td>
<td>0.66 (0.47 to 0.93)</td>
<td>3</td>
</tr>
</tbody>
</table>

*Mantel Haenszel fixed method
†Comparison not included in Cochrane systematic review by Gluud, 2012
‡Compared intervention group of TXA plus lansoprazole with control group of lansoprazole alone