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Transfusion Medicine | LETTER TO THE EDITOR

Extending evidence for the use of tranexamic acid from traumatic haemorrhage to other patients with major bleeding: do we need more than one haemorrhage protocol? The case of gastrointestinal bleeding

Dear Sir,

Haematologists, and specifically those with responsibility for transfusion including through the Hospital Transfusion Committee, have an important role to provide direction and guidance for the appropriate resuscitation of patients with major bleeding. Major bleeding is an emergency, and all hospitals should have local policies for managing patients with significant haemorrhage, which are referred to as massive haemorrhage protocols. We wish to highlight one important issue regarding the broader use of tranexamic acid (TXA) as part of a massive haemorrhage protocol: Should all types of bleeding patients be managed using the same policies typically developed initially for use in trauma?

It is now well recognised that many different causes of bleeding other than due to trauma often present in the emergency department including gastrointestinal (GI). Acute upper GI bleeding remains a common reason for emergency hospital admission with an annual incidence of 50–150/100 000 adults (Rockall *et al.*, 1995; Blatchford *et al.*, 1997). TXA, given its good safety profile, ease of administration and low cost, is considered one of the components of most major haemorrhage protocols. Whilst there has been a marked increase in use of TXA for a variety of indications, we have reservations about a broader extrapolation to all groups of bleeding patients beyond use in trauma. This issue has been a significant topic of discussion during the running of the 'HALT-IT' (Haemorrhage ALleviation with Tranexamic acid – InTestinal system) trial, as described below.

Following on from the results of CRASH2, all trauma patients with severe bleeding should be treated with TXA (The CRASH-2 Collaborators, 2010). Timing is critical, given the recognition that death directly from bleeding occurs within a few hours and that CRASH2 indicated that TXA is beneficial only when given within 3 h after injury (The CRASH-2 Collaborators, 2011); after 3 h, use of TXA was associated with a greater risk of death due to bleeding (The CRASH-2 Collaborators, 2011). Additionally, TXA was shown to be equally effective for every category of trauma severity (Perel *et al.*, 2013). The CRASH2 population consisted of adults with average age of 34 years (The CRASH-2 Collaborators, 2010). They were likely to have less co-morbidity, particularly cardiovascular or cerebrovascular disease.

There is evidence of excessive fibrinolysis both in patients with trauma-related bleeding and GI bleeding (Poller & Thomson, 1973; Lawson & Murphy, 2004), which provides biological plausibility of a potential benefit of TXA in both conditions. However, patients with GI bleeding are usually older and have a more underlying co-morbidities in comparison to patients with traumatic bleeding; in a UK nationwide audit, the mean age of patients with GI bleeding was 64 years, with 18% having a history of ischaemic heart disease and 8% a previous stroke (Hearnshaw *et al.*, 2011). Patients with GI bleeding, which is often intermittent, usually present several hours after the onset of symptoms. In a survey in patients with variceal bleeding, about 40% of patients were admitted to hospital after 12 h from the onset of symptoms (Charpignon *et al.*, 2007). For these reasons, it cannot be excluded that harms, including thrombotic events, from the use of TXA might be greater in patients with GI bleeding compared to trauma patients. But a treatment such as TXA might help prevent GI re-bleeding, which is associated with a five-fold increased risk of death (D'Amico *et al.*, 2003; Barkun *et al.*, 2004; Carbonell *et al.*, 2004).

A recent update of a systematic review identified nine randomised comparisons from eight clinical trials of the use of TXA in upper GI bleeding, and none in lower GI bleeding (Manno *et al.*, 2014). The pooled results showed a reduction in the risk of death in patients receiving TXA. However, the poor methodological quality of some of the studies and the inadequate sample size of trials, even when combined in the meta-analysis, suggests the possibility of an unreliable result. Moreover, only three trials reported data on adverse events. Specifically, the risk of thromboembolic events was about 1% overall and may be higher in TXA treated patients (Gluud *et al.*, 2012).

With the uncertainty in both size of treatment effect and in risk of bias from previous studies, the 'HALT-IT' (Haemorrhage ALleviation with Tranexamic acid – InTestinal system) trial has been funded by National Institute for Health Research (NIHR) to establish definitely the effect of TXA on mortality and morbidity (including re-bleeding and thromboembolic events) in patients with significant GI bleeding (haltit.Lshtm.ac.uk). HALT-IT is a pragmatic, randomised, double blind, placebo controlled trial aiming to recruit 8000 patients with significant upper or lower GI bleeding. The diagnosis of significant bleeding is clinical but includes patients with hypotension, tachycardia, or those

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likely to need transfusion, urgent endoscopy or surgery. The fundamental eligibility criterion is the responsible clinician's 'uncertainty' as to whether or not to use TXA in a particular patient with GI bleeding. If the clinician believes there is a clear indication for, or clear contraindication to, TXA use, the patient should not be randomised. If a clinician believes that TXA would be useful as a rescue medication should a patient deteriorate, then the patient should not be enrolled since the doctor is not substantially uncertain about the effects of the study medication.

The trial is a multi-disciplinary effort, involving emergency physicians, gastroenterologists, surgeons and haematologists. Recruitment is proceeding well and ahead of target in UK. More than 60 hospitals across the country are actively recruiting patients. An essential requisite to join the trial is that local clinicians treating GI bleeding have clinical equipoise about the use of TXA for GI bleeding.

The HALT-IT trial offers the opportunity to generate high quality evidence on the effectiveness and safety of TXA in patients with GI bleeding. We believe it is not appropriate to directly extrapolate findings from research in trauma to GI bleeding, which affects a very different age population, with different co-morbidities and where different pathophysiological mechanisms of injury apply. Doctors might have different opinions about the use of TXA in different patient groups with major bleeding, but only evidence coming from adequately powered high quality clinical trials will solve the uncertainty and improve clinical practice. Other aspects of resuscitation, such as red cell transfusion in patients with varying degrees of severity of blood loss and anaemia, also require more evidence to weigh up the risk benefit profile in different patient groups (Villanueva *et al.*, 2013). Ultimately, our aim is to define the optimal treatment protocols for different causes of haemorrhage modified by patient characteristics.

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CONFLICT OF INTEREST

All authors declare no conflict of interest.

REFERENCES

Barkun, A., Sabbah, S., Enns, R. RUGBE Investigators *et al.* (2004) The Canadian Registry on Nonvariceal Upper Gastrointestinal Bleeding and Endoscopy (RUGBE): endoscopic hemostasis and proton pump inhibition are associated with improved outcomes in a real-life setting. *American Journal of Gastroenterology*, **99**, 1238–1246.

Blatchford, O., Davidson, L.A., Murray, W.R., Blatchford, M. & Pell, J. (1997) Acute upper gastrointestinal haemorrhage in west of Scotland: case ascertainment study. *BMJ*, **315**, 510–514.

Carbonell, N., Pauwels, A., Serfaty, L., Fourdan, O., Levy, V.G. & Poupon, R. (2004) Improved survival after variceal bleeding in patients with cirrhosis over the past two decades. *Hepatology*, **40**, 652–659.

Charpignon, C., Oberti, F., Bernard, P. French National Working Group on Portal, H. *et al.* (2007) Management practices for gastrointestinal hemorrhage related to portal hypertension in cirrhotic patients: evaluation of the impact of the Paris consensus workshop. *Gastroentérologie Clinique et Biologique*, **31**, 970–974.

D'Amico, G., De Franchis, R. & Cooperative Study Group (2003) Upper digestive bleeding in cirrhosis. Post-therapeutic outcome and prognostic indicators. *Hepatology*, **38**, 599–612.

Gluud, L.L., Klingenberg, S.L. & Langholz, E. (2012) Tranexamic acid for upper gastrointestinal bleeding. *Cochrane Database Systematic Reviews*, **1**, CD006640.

Hearnshaw, S.A., Logan, R.F., Lowe, D., Travis, S.P., Murphy, M.F. & Palmer, K.R. (2011) Acute upper gastrointestinal bleeding in the UK: patient characteristics, diagnoses and outcomes in the 2007 UK audit. *Gut*, **60**, 1327–1335.

Lawson, J.H. & Murphy, M.P. (2004) Challenges for providing effective hemostasis in surgery and trauma. *Seminars in Hematology*, **41**, 55–64.

Manno, D., Ker, K. & Roberts, I. (2014) How effective is tranexamic acid for acute gastrointestinal bleeding? *BMJ*, **348**, g1421.

Perel, P., Prieto-Merino, D., Shakur, H. & Roberts, I. (2013) Development and validation of a prognostic model to predict death in patients with traumatic bleeding, and evaluation of the effect of tranexamic acid on mortality according to baseline risk: a secondary analysis of a randomised controlled trial. *Health Technology Assessment*, **17**, 1–45, v–vi.

Poller, L. & Thomson, J. (1973) Evidence for a relationship between fibrinolysis and haematemesis. *British Journal of Haematology*, **24**, 664.

Rockall, T.A., Logan, R.F., Devlin, H.B. & Northfield, T.C. (1995) Incidence of and mortality from acute upper gastrointestinal haemorrhage in the United Kingdom. Steering Committee and members of the National Audit of Acute Upper Gastrointestinal Haemorrhage. *BMJ*, **311**, 222–226.

The CRASH-2 Collaborators (2010) 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*, **376**, 23 – 32.

The CRASH-2 Collaborators (2011) The importance of early treatment with tranexamic acid in bleeding trauma patients: an exploratory analysis of the CRASH-2 randomised controlled trial. *Lancet*, **377**, 1096 – 1101, 1101 e1091 – e1092.

Villanueva, C., Colomo, A., Bosch, A. *et al.* (2013) Transfusion strategies for acute upper gastrointestinal bleeding. *New England Journal of Medicine*, **368**, 11 – 21.