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Review Article

The current place of tranexamic acid in the management of bleeding

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Summary

There has been an explosion of interest in the ability of tranexamic acid to reduce morbidity and mortality in surgical and traumatic bleeding. Tranexamic acid has been shown to reduce mortality due to traumatic bleeding by a third, without apparent safety issues. It is now clearly established that intravenous tranexamic acid reduces blood loss in patients with surgical bleeding and the need for transfusion. It can also be used topically to reduce bleeding. Its use is being explored further in large pragmatic trials in traumatic head injury, postpartum haemorrhage and in upper gastro-intestinal haemorrhage. There are few side effects from the use of tranexamic acid except when administered in high dose where neurological events have been noted, possibly relating to tranexamic acid interfering with cerebral GABA and glycine receptors. However, clinical studies suggest that there is no increased efficacy in using a higher dose, and that a dose of 1 g intravenously in an adult patient has maximal efficacy, which is not increased by higher doses. The CRASH-2 trauma trial clearly showed no increase in thrombotic events after its use in trauma, indeed there was a significant reduction in myocardial infarction. However, trials of tranexamic acid in surgery have failed to adequately study its effects on the risk of postoperative venous and possible reduction in arterial thromboembolism, and this needs to be the subject of future research.

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Introduction

In the last decade, there has been an explosion of interest in the utility of tranexamic acid (TA) in reducing bleeding, fuelled, in particular, by the publication of CRASH-2 [1], the largest trauma trial ever conducted. This has also stimulated interest in the role of fibrinolysis in bleeding. This article presents an overview of our current understanding as to where TA may have clinical benefit, the appropriate dose and possible side effects.

Pharmacology of TA

Tranexamic acid (trans-4-(aminomethyl) cyclohexanecarboxylic acid) is a synthetic derivative of the amino acid lysine that competitively inhibits the activation of plasminogen to the serine protease, plasmin, via binding to kringle domains. Tranexamic acid is also a competitive inhibitor of tissue plasminogen activator. It blocks the lysine-binding sites of plasminogen, resulting in inhibition of plasminogen activation and fibrin binding to plasminogen and therefore impairment of fibrinolysis [2].

Tranexamic acid can also directly inhibit plasmin activity, but higher doses are required to reduce plasmin formation. Tranexamic acid is about ten times more potent in vitro than aminocaproic acid, and binds more strongly than aminocaproic acid to both the strong and weak receptor sites of the plasminogen

molecule in a ratio corresponding to the difference in potency between the compounds. Tranexamic acid is distributed throughout all body tissues and the plasma half-life is 120 min.

The efficacy of TA in reducing traumatic bleeding

The largest trial to date of antifibrinolytics: the Clinical Randomisation of Antifibrinolytics in Significant Haemorrhage (CRASH-2) trial, assessed the effects of early administration of TA in trauma patients with, or at risk of, substantial bleeding [1]. A total of 20 211 trauma patients from 40 countries were randomly assigned within 8 h of injury to either TA (1 g load, then 1 g over 8 h) or placebo. The primary outcome was in-hospital mortality within 4 weeks of injury. All-cause mortality was significantly reduced with TA (14.5% vs 16%; relative risk (RR) 0.91, 95% CI 0.85–0.97; p = 0.0035). The data from CRASH-2 showed that, following the second day, bleeding is not the main cause of mortality, and was ascribed to head injury, multi-organ failure and vaso-occlusive complications, all of which were reduced, although all except myocardial infarction were non-significantly reduced in those receiving TA. However, the critical question was whether there was a reduction in bleeding deaths, and indeed, a significant reduction in death due to bleeding by one-third was seen. The excitement about the application of the findings of CRASH-2 is that death due to traumatic bleeding is a global problem, and if TA was given to all those with, or at risk of, traumatic bleeding, this would result in a worldwide reduction in the number of deaths of 120 000 per annum. The response in the UK has been positive, with NHS England ensuring that all ambulances and paramedics carry TA; moreover TA needs to be administered in patients 'receiving blood products within 3 h of injury' under the Major Trauma Best Practice Tariff [3].

Despite the reduction in mortality due to bleeding, TA did not reduce transfusion requirements. Why might this be? The management of blood loss during trauma is not fine-tuned to compensate for losses as it is in surgical practice; blood is given empirically and blood losses not accurately measured. Also, investigators were asked to use their normal practice and the availability of blood components is variable between the 40 countries involved in the study – it is widely recognised that blood transfusion practice varies widely. We also hypothesised that a proportion of the reduction in deaths was not due to reduced bleeding but other mechanisms, perhaps due to the anti-inflammatory and/or anti-thrombotic effects of TA [4].

Timing of TA administration is important. Further analysis of CRASH-2 showed that treatment given in the first 3 h reduced the risk of death due to bleeding, with RR reduction in the first hour of 0.68 (95% CI 0.57–0.82; p < 0.0001) and 0.79 (95% CI 0.64–0.97; p = 0.03) between 1 and 3 h. However, treatment given after 3 h seemed to increase death due to bleeding, with a RR of 1.44 (95% CI 1.12–1.84; p = 0.004) [5]. Thus, TA should be given as early as possible to bleeding trauma patients. For trauma patients admitted late after injury, TA is less effective, and could be harmful.

Efficacy of TA in reducing surgical bleeding

Since the withdrawal of aprotinin, TA has been widely used to reduce bleeding in cardiac surgery, but it is now also used in other types of surgery. In 2007, a systematic review of randomly assigned trials assessing TA in elective surgery identified 53 studies that included 3836 patients [6]. Tranexamic acid reduced the need for blood transfusion by a third (RR 0.61, 95% CI 0.54–0.70). A further systematic review in 2012 [7], reflecting the increased interest in TA over the intervening years, identified 129 trials that included 10 488 patients, carried out between 1972 and 2011. In this meta-analysis, TA reduced the probability of receiving a blood transfusion by a third (RR 0.62, 95% CI 0.58–0.65; p < 0.001). This effect remained when the analysis was restricted to trials using adequate allocation concealment (RR 0.68, CI 0.62–0.74; p < 0.001). Fewer deaths occurred in the TA group (RR 0.61, CI 0.38–0.98; p = 0.04), although when the analysis was restricted to trials using adequate concealment there was considerable uncertainty (RR 0.67, CI 0.33–1.34; p = 0.25). The authors concluded that cumulative meta-analysis showed reliable evidence that TA reduces the need for transfusion.

Another systematic review of 104 randomly assigned trials examined whether the effect of TA on blood loss varies with the extent of surgical bleeding. The results suggest that, despite variation in the magnitude of blood loss between procedures and the heterogeneity of the studies included, the use of TA was associated with an overall reduction in surgical bleeding by about a third. This reduction in bleeding with TA is almost identical to the reduction in the risk of receiving a blood transfusion with TA suggesting, as expected in the closely monitored environment of an operating theatre, that unlike traumatic bleeding in CRASH-2, blood transfusion use was closely titrated to blood loss [8].

Efficacy of TA in postpartum haemorrhage

A Cochrane review in 2010 [9] concluded that TA decreased postpartum blood loss after vaginal delivery and caesarean section, but since there were only two randomised controlled trials, which were small and of unclear quality, further studies were needed to establish efficacy and safety. In a subsequent study Xu et al. [10] conducted a randomly assigned, double-blind, case–control study of TA 10 $ml.kg^{-1}$ vs placebo in 174 primiparous patients undergoing caesarean section (CS). Blood loss up to 2 h postpartum was significantly lower ($p < 0.01$) in the TA group (mean (SD) 46.6 (42.7) ml) than in the control group (84.7 (80.2) ml), but the blood loss in the period from placental delivery to the end of CS did not differ between the TA and control groups ($p = 0.17$). No significant abnormal vital signs were observed after TA administration. Ducloy et al. [11] studied the use of high-dose TA in a randomly assigned, controlled, multicentre, open-label trial. Women with postpartum haemorrhage (PPH) > 800 ml following vaginal delivery were randomly assigned to receive TA (loading dose 4 g over 1 h, then infusion of 1 $g.h^{-1}$ over 6 h) or not. Blood loss between enrolment and 6 h later was significantly lower in the TA group (median (IQR) 173 (59–377) ml) than in controls (221 (105–564) ml), $p = 0.041$. In the TA group, bleeding duration was shorter and progression to severe PPH was less frequent than in controls ($p < 0.03$). Red cell transfusion was needed in 93% of women in the TA group vs 79% of controls ($p = 0.016$). This study is the first to demonstrate that high-dose TA can reduce blood loss and maternal morbidity in women with PPH. However this and previous studies were not adequately powered to address safety issues, notably the rate of venous thrombo-embolism (VTE) postpartum. Postpartum women are at high risk of VTE, it remains one of the major causes of maternal mortality, and there is concern that using an antifibrinolytic drug may increase this risk.

The WOMAN study [12], is a large, pragmatic, randomly assigned, double-blind, placebo-controlled trial designed to determine the effect of early administration of TXA on mortality, hysterectomy and other morbidities (surgical interventions, blood transfusion, risk of non-fatal vascular events) in women with clinically diagnosed PPH. The use of health services and safety, especially thrombo-embolic effect will be assessed. Treatment entails a dose of TA (1 g by intravenous injection) or placebo (sodium chloride 0.9%) given as soon as possible after randomisation. A second dose may be given after 30 min if bleeding continues, or if it stops and restarts within 24 h after the first dose. The main analyses will be on an 'intention to treat' basis, irrespective of whether the allocated treatment was received or not. The study aims to recruit 20 000 women (and has recruited over 14 000 at time of writing), and will have over 90% power to detect a 25% reduction from 4% to 3% in the primary endpoint of mortality or hysterectomy; it is due to report in 2016/7.

Topical use of TA

There is reliable evidence that topical application of TA reduces bleeding and blood transfusion in surgical patients; however, the effect on the risk of thrombo-embolic events is uncertain [13]. Furthermore, high-quality trials are warranted to resolve these uncertainties before topical TA can be recommended for routine use.

Other areas where TA is being trialled

There are inadequate studies to ascertain whether TA will be beneficial in reducing gastro-intestinal (GI) bleeding and mortality, and it is debatable whether the results of CRASH-2 should be extrapolated from

trauma to GI bleeding. Thus, an ongoing trial is addressing this research question. The haemorrhage alleviation with TA – intestinal symptoms (HALT-IT) is currently randomising 8000 patients with acute upper GI haemorrhage to TA vs placebo [14]. The CRASH-3 trial is an international, multicentre, pragmatic, randomly assigned, double-blind, placebo-controlled trial to quantify the effects of the early administration of TA on death and disability in patients with traumatic brain injury. Ten thousand adult patients will be randomly assigned to receive TA or placebo. Treatment will entail a 1 g loading dose followed by a 1 g maintenance dose over 8 h [15].

Dose of TA

The original studies by Horrow et al. showed that, in cardiac surgery, a dose of TA of 10 $mg.kg^{-1}$ followed by 1 $mg.kg^{-1}.h^{-1}$ decreased bleeding during cardiac surgery and larger doses did not produce haemostatic benefit [16, 17]. CRASH-2 used this information to produce an empirical dose to provide adequate plasma levels to have an antiplasmin effect in adults. The meta-analysis by Ker et al. [8] also suggested that a dose of 1 g produced a reduction in bleeding that was not improved by giving higher doses. This study showed that a total dose of 1 g was likely to be sufficient for most adults and there was no evidence to support higher doses.

Since 2010, there have been a number of articles describing seizures with high-dose TA; using doses much greater than the original Horrow recommendations [17, 18]. In an elegant set of studies, Lecker et al. [19] showed there is structural similarity between the TA and inhibitory neurotransmitter-gated Cl^- channel glycine receptors, and demonstrated that TA inhibits glycine receptors and binds competitively to GABA type-A receptors. They proposed that the higher rate of TA-related seizures seen in cardiac surgery may relate to disruption of the blood brain barrier by cerebral emboli. However, it may also be that cardiac surgery is one of the few areas where very high doses of TA have been used. Anaesthetic agents with glycine receptor agonist properties such as isoflurane or propofol may be uniquely suited to prevent such seizures after surgery; although ultimately limiting the dose of TA to the original dose suggested Horrow appears as safe and efficacious as a higher dose.

Thrombotic risk

CRASH-2 showed that TA significantly reduced the risk of myocardial infarction, and had no effect on the rate of venous thrombo-embolism, reassuring physicians that it is safe to use in a trauma setting. Although there is strong evidence that TA reduces blood transfusion in surgery, there is still uncertainty as to whether TA may be associated with an increased risk of arterial and venous thrombo-embolism, and this uncertainty limits its widespread use. In a large meta-analysis [7], the effect of TA on myocardial infarction (0.68, CI 0.43–1.09; p = 0.11), stroke (1.14, CI 0.65–2.00; p = 0.65), deep vein thrombosis (0.86, CI 0.53–1.39; p = 0.54), and pulmonary embolism (0.61, CI 0.25–1.47; p = 0.27) was uncertain. A newly published analysis of the use of TA in hip and knee replacement in the USA has suggested that there is no increased risk of vascular occlusive events in this group of patients [20].

The effect of TA on thrombo-embolic events and mortality requires further attention. The ongoing Aspirin and Tranexamic Acid for Coronary Artery Surgery trial [21] should help resolve uncertainties around cardiac surgery, but there is still a need for a large pragmatic trial in other surgical patients. Furthermore, there is an exciting suggestion from CRASH-2 that the use of TA could reduce death due to postoperative myocardial infarction [22], making TA a highly cost-effective way of improving surgical safety. It is timely to resolve this uncertainty in an adequately powered randomly controlled trial.

Acknowledgements

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Competing interests

No other conflicts of interest.

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