Should antifibrinolytics be given in all patients with trauma?

Marcel Levi

Purpose of review
Hemorrhage is the second most important cause of death in patients with trauma, contributing to approximately 30% of trauma-related mortality. Pharmacological prohemostatic agents may be useful adjunctive treatment options in patients with severe blood loss.

Recent findings
Tranexamic acid was evaluated in a large international randomized controlled study in patients with trauma and severe blood loss. The drug was shown to reduce death due to bleeding, provided the treatment was given within 3 h after injury. Tranexamic acid treatment did not result in serious adverse events nor thrombotic complications.

Summary
In view of this efficacy and safety of this relatively cheap and simple drug, it may be recommended to put tranexamic acid in the first (maybe even prehospital) line of management of patients with severe traumatic hemorrhage.

Keywords
antifibrinolytics, hemorrhage, prohemostatic drugs, tranexamic acid, trauma

INTRODUCTION
Bleeding is a frequently occurring clinical problem. A substantial number of hospital admissions in medical wards is related to bleeding and perioperative bleeding is one of the most frequent complications of surgery [1**]. Bleeding is of particular importance in trauma and is the second most important cause of death in trauma patients, contributing to approximately 30% of trauma-related mortality [2]. Trauma-related coagulopathy proceeds via a myriad of mechanisms, including loss of factors and platelets due to massive bleeding, acidosis and hypothermia further compromising the coagulation system, dysregulation of mediatory pathways, such as the activated protein C system and fibrinolysis, and systemic activation of thrombin generation [3*].

Management of bleeding consists of local control measures to retain adequate circulation, and proper transfusion procedures [4]. In addition to these strategies, prohemostatic treatment may, in some cases, support the treatment of (severe) bleeding. Pharmacological agents that are capable of promoting hemostasis or fibrin formation, or can block fibrinolytic activity, may interfere in the balance between activation of coagulation and physiological anticoagulation. This strategy may be useful in the prevention and treatment of bleeding in patients with coagulation defects but also in patients with an a priori normal coagulation system, who experience severe (postoperative) bleeding or are to undergo procedures known to be associated with major blood loss [5].

The safety of prohemostatic therapy also deserves some consideration. Interfering in the balance between coagulant and anticoagulant mechanisms can indeed result in undesirable adverse effects. The best illustration may be the higher risk of bleeding in patients receiving anticoagulant therapy. Conversely, prohemostatic agents may, at least theoretically, predispose for thrombotic complications. The occurrence of such complications are fortunately relatively rare. Obviously, the expected benefit of the application of prohemostatic agents

Department of Medicine, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands

Correspondence to Marcel Levi, MD, Academic Medical Center, University of Amsterdam, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands. Tel: +31 20 5662109; e-mail: mailto:m.m.levi@amc.uva.nl

Curr Opin Anesthesiol 2012, 25:000–000
DOI:10.1097/ACO.0b013e3283532b29
It has been calculated that universal use of tranexamic acid (Cyklokapron, Pfizer, New York, NY, USA) is at least 10 times more potent than e-aminocaproic acid (Amicar, Xanodyne Pharmaceuticals Inc., Newport, KY, USA). Tranexamic acid was shown to be effective in reducing blood loss, transfusion requirement, and prevention of re-exploration due to ongoing hemorrhage in a variety of clinical settings, including cardiac surgery, major orthopaedic surgery, and gynaecological conditions [11–13].

A recently conducted large randomized trial with tranexamic acid in 20211 patients (admitted to 274 hospitals in 40 different countries) with major trauma and with, or at risk of, severe hemorrhage showed a reduction of mortality in patients who received tranexamic acid compared with placebo [9**]. Patients were treated within 8 h of injury with either tranexamic acid (1 g over 10 min followed by another gram over 8 h) (n = 10.096), or placebo (n = 10.115). All-cause mortality at 4 weeks after admission was 14.5% in the tranexamic acid group as compared with 16% in the placebo group [relative risk (RR) 0.91, 95% confidence interval (CI) 0.85–0.97, P = 0.0035]. The risk of death due to haemorrhage was reduced from 5.7% in controls to 4.9% in the tranexamic acid-treated patients (RR 0.85%, 95% CI 0.76–0.96, P = 0.0077). Interestingly, there were no detectable differences in the rate of transfusion and the need for surgical (re)exploration between the two groups. Tranexamic acid was remarkably well tolerated in this study. In the tranexamic acid group, 168 patients (1.7%) had occlusive vascular events compared with 201 patients (2.0%) in the placebo group. There were also no differences in deaths due to vascular complications between the two groups.

In an additional analysis, the authors found strong evidence that early administration of tranexamic acid was relatively more favourable in comparison with administration at a later time after trauma [14*]. Early (<1 h) treatment with tranexamic acid reduced the rate of death due to bleeding to 5.3% compared with 7.7% in the placebo group (RR 0.68, 95% CI 0.57–0.82, P < 0.0001), whereas this RR decreased when the drug was given 1–3 h after trauma to 0.79 (95% CI 0.64–0.97, P = 0.03) and was 1.44 (95% CI 1.12–1.84, P = 0.004) when tranexamic acid was given later than 3 h. There was no evidence that the effect of tranexamic acid on death due to bleeding was influenced by other factors, including Glasgow Coma Score, type of injury, or SBP. Another analysis concerned the subgroup of patients with traumatic brain injury. In a nested case–control study, the authors studied 270 patients who also had traumatic brain injury in addition to their extracranial bleeding due to trauma.

**KEY POINTS**

- Bleeding is of particular importance in trauma and is the second most important cause of death in trauma patients, contributing to approximately 30% of trauma-related mortality.
- Prohemostatic strategies, including antifibrinolytic agents, may support the treatment of severe bleeding in trauma patients.
- Randomized controlled trials showed a reduction of mortality in patients with major trauma and with, or at risk of, severe hemorrhage that received the antifibrinolytic agent tranexamic acid.
- Tranexamic acid is remarkably well tolerated in patients with trauma and is not associated with thrombotic complications or other adverse events.
- It has been calculated that universal use of tranexamic acid may result in the averting of death in more than 70,000 trauma patients each year worldwide.

Antifibrinolytic treatment can interfere with the coagulation system or promote primary hemostasis [1***,6–8]. One of the best studied prohemostatic interventions is antifibrinolytic treatment. Recently, the use of the antifibrinolytic agent tranexamic acid was shown to reduce mortality in trauma patients with excessive blood loss in a large international controlled multicenter trial [9**]. We will briefly report on the findings in this trial and subsequently try to answer the question whether all patients with trauma should be treated with tranexamic acid.

**ANTIFIBRINOLYTIC TREATMENT IN TRAUMA**

Agents that exert antifibrinolytic activity are aprotinin and the group of lysine analogues [10]. Lysine analogues, that is, e-aminocaproic acid and tranexamic acid are potent inhibitors of fibrinolysis [10]. The antifibrinolytic action of lysine analogues is based on the competitive binding of these agents to the lysine-binding sites of a fibrin clot, thereby competing with the binding of plasminogen. Impaired plasminogen binding to fibrin delays the conversion of plasminogen to plasmin and subsequent plasmin-mediated fibrinolysis, which then proceeds at an inefficient and slow rate. Subtle molecular variations between different lysine analogues may have important consequences for their fibrinolysis-inhibiting capacity. Indeed, tranexamic acid is at least 10 times more potent than e-aminocaproic acid (Amicar, Xanodyne Pharmaceuticals Inc., Newport, KY, USA). Tranexamic acid was shown to be effective in reducing blood loss, transfusion requirement, and prevention of re-exploration due to ongoing hemorrhage in a variety of clinical settings, including cardiac surgery, major orthopaedic surgery, and gynaecological conditions [11–13].
focused at improvement of coagulation interventions, as well as strategies specifically using different plasma expanders, and hemodynamic blood-saving strategies, resuscitation protocols trauma. Other clinical interventions have not and death due to bleeding in patients with severe lytic agent tranexamic acid results in less bleeding overwhelmingly shows that administration of the antifibrinolytic drug in the first line of treatment of with tranexamic acid and in 9% of patients in the control group. Death occurred in 11% of tranexamic acid-treated patients versus 18% in control patients (adjusted odds ratio 0.47, 95% CI 0.21–1.04).

PUTTING THE CRASH-2 DATA IN PERSPECTIVE

The Clinical Randomization of an Antifibrinolytic in Significant Hemorrhage (CRASH)-2 study convincingly shows that administration of the antifibrinolytic agent tranexamic acid results in less bleeding and death due to bleeding in patients with severe trauma. Other clinical interventions have not been proven to be effective in this setting, including blood-saving strategies, resuscitation protocols using different plasma expanders, and hemodynamic interventions, as well as strategies specifically focused at improvement of coagulation [16,17]. In a meta-analysis of four studies investigating antifibrinolytic agents in patients with acute traumatic injury and (high risk of) bleeding, the authors found that tranexamic acid reduced the risk of death by 10–15%. Obviously, the results in this meta-analysis were strongly driven by the CRASH-2 study results. In an interesting cost-effectiveness study in three types of countries participating in the CRASH-2 study, the investigators were able to demonstrate that the incremental cost per life year gained by the administration of tranexamic acid was US$ 48, 66, and 64 in Tanzania, India, and the UK, respectively [18]. Based on these calculations, it may be concluded that tranexamic acid was highly cost-effective, regardless of the setting in high-income or low-income countries.

It may be argued that whereas the RR reduction in traumatic death caused by tranexamic acid was impressive, the absolute risk reduction was modest. Although this may be true, a 1.5% reduction in death due to trauma translates to the saving of a very large number of people worldwide, as death due to trauma is very prevalent. It has been calculated that universal use of tranexamic acid may result in the averting of death in more than 70,000 patients each year worldwide [19]. The lack of any effect of tranexamic acid on transfusion rates remains puzzling. However, one needs to realize that it may well be that surviving patients received more transfusion than patients who died in the early phase after trauma [20]. This ‘survivor bias’ could only be properly analysed if the data would allow us to show time-related transfusion rates or (excessive) transfusion-free survival rates, information which is probably not available. Another (not unlikely) possibility is that transfusion protocols are not very well tailored to the bleeding status of the patient.

CONCLUSION

Prohemostatic interventions appear to be effective in reducing perioperative blood loss and transfusion requirements in specific situations and may be helpful adjuncts in the management of severe spontaneous and postoperative bleeding. Early antifibrinolytic treatment with tranexamic acid (1 g as a bolus in 10 min followed by another gram in 8 h intravenously) was clearly shown to be of benefit in patients with severe trauma and major blood loss. Analysis of trial results indicate that this treatment should be given within 3 h after trauma. Remarkably, the administration of tranexamic acid was well tolerated and did not result in major adverse events or thrombotic complications. This seems to be another benefit of this intervention, in contrast to other prohemostatic strategies that may carry the risk of thrombosis [21]. In addition, the treatment with tranexamic acid is simple and relatively cheap, contributing to a beneficial cost-effectiveness, also in resource-poor settings.

The next challenge is to translate these favourable findings from clinical studies into real-life clinical practice [22]. There are many arguments for placing tranexamic acid in the first line of defence in patients with severe traumatic injury and blood loss. In some settings, this may mean prehospital administration of the drug, which could be facilitated by the uncomplicated storage of the drug. If prehospital administration is not possible or required, it may be administered in the emergency room provided that the time window of 3 h after injury has not passed. Treatment should be initiated on the basis of clinical findings and regardless of laboratory tests, which are anyway not very helpful in the early stage of the management of traumatic bleeding. The inclusion criteria of the CRASH-2 study are sufficiently helpful for routine clinical practice to guide its administration and it is not likely that a certain amount of ‘overtreatment’ would result in direct harm for the patient. Taken together, there seems to be sufficient evidence to put tranexamic acid in the first line of treatment of patients who present with major blood loss after trauma.

Acknowledgements

None.
Conflicts of interest
There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:
* of special interest
** of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 000–000).


8. Sydenham E. Thousands of lives could be saved using tranexamic acid for patients with bleeding trauma. Inj Prev 2011; 17:211. Article extrapolating the benefit of universal use of tranexamic acid in trauma patients.


