Tranexamic acid as part of remote damage-control resuscitation in the prehospital setting: A critical appraisal of the medical literature and available alternatives

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BACKGROUND: Hemorrhage remains the leading cause of preventable trauma-associated mortality. Interventions that improve prehospital hemorrhage control and resuscitation are needed. Tranexamic acid (TXA) has recently been shown to reduce mortality in trauma patients when administered upon hospital admission, and available data suggest that early dosing confers maximum benefit. Data regarding TXA implementation in prehospital trauma care and analyses of alternatives are lacking. This review examines the available evidence that would inform selection of hemostatic interventions to improve outcomes in prehospital trauma management as part of a broader strategy of "remote damage-control resuscitation" (RDCR).

METHODS: The medical literature available concerning both the safety and the efficacy of TXA and other hemostatic agents was reviewed.

RESULTS: TXA use in surgery was studied in 129 randomized controlled trials, and a meta-analysis was identified. More than 800,000 patients were followed up in large cohort study. In trauma, a large randomized controlled trial, the CRASH-2 study, recruited more than 20,000 patients, and two cohort studies studied more than 1,000 war casualties. In the prehospital setting, the US, French, British, and Israeli militaries as well as the British, Norwegian, and Israeli civilian ambulance services have implemented TXA use as part of RDCR policies.

CONCLUSION: Available data support the efficacy and the safety of TXA. High-level evidence supports its use in trauma and strongly suggests that its implementation in the prehospital setting offers a survival advantage to many patients, particularly when evacuation to surgical care may be delayed. TXA plays a central role in the development of RDCR strategies. (*J Trauma Acute Care Surg*. 2015;78: S70–S75.

KEY WORDS: Tranexamic acid; hemorrhage; military; prehospital; resuscitation.

During the last two decades, the prognosis of battle casualties has improved mainly because of the deployment of comprehensive military health care systems.[1–3] The case-fatality rate (ratio of number killed to injured, representing the probability of dying after experiencing a battle injury) has fallen from 25% to 30% to 10% to 15% or less.[4,5] Some of this progress could be credited to the adoption of methodological approaches to combat casualty care, emphasizing the importance of early, goal-directed care, such as the implementation of Tactical Combat Casualty Care (TCCC) in the US military since 2003[6] and thereafter in numerous Western armies.[7] A sharp decrease in the proportion of killed in action (casualties dying before reaching a medical treatment facility) followed[2] and more severely injured patients arrive alive at higher levels of care. The percentage of patients who died of their wounds has only slightly increased, from 3% to 5%.[8]

Nonetheless, nearly 90% of all battlefield fatalities die before reaching a surgical facility, and 25% of these deaths were retrospectively deemed to be potentially survivable.[9] Hemorrhage caused 90% of the potentially survivable deaths.[9] Therefore, every means aimed at mitigating hemorrhage in the field should be implemented as part of the prehospital casualty care strategy and integrated within the "remote damage-control resuscitation" (RDCR) concept. RDCR represents a combination of hypotensive and hemostatic resuscitation performed as far forward as possible, near the point of injury.[10]

Strengthening prehospital medical capabilities has become a core issue as operations shift from Afghanistan to the Sahel region of Africa and other dispersed, lightly supported areas of operation where evacuation times are significantly prolonged.

Key aspects of RDCR such as blood transfusion in the field and hypotensive resuscitation have been described elsewhere;[10–13] we will focus on the use of tranexamic acid (TXA) in the prehospital setting. TXA, a derivative of the amino acid lysine, hinders fibrinolysis by inhibiting the activation of plasminogen to plasmin,[14] thus strengthening clots and reducing bleeding. Several questions regarding TXA use in the prehospital environment will be addressed:

1. Other options for hemostatic interventions in the field?
2. Data supporting efficacy of using TXA early?
3. Safety data?
4. Reports of TXA prehospital use?

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METHODS

To address these questions, the medical literature available concerning both the safety and the efficacy of TXA and other hemostatic agents was reviewed. When available, quantitative analysis of meta-analyses were used and rated according to the GRADE method.[15]

What Are the Hemostatic Therapies Available for RDCR?

Antifibrinolytic Agents

Three antifibrinolytic agents that reduce hemorrhage by inhibiting fibrinolysis are described in the literature, namely, aprotinin, TXA, and ε-aminocaproic acid.[16] Aprotinin was withdrawn from the market in 2007 because of safety concerns. Although its marketing authorization was recently reinstated by the European Medicines Agency,[17] it is not widely used. Two meta-analyses have examined the use of antifibrinolytics in the perioperative setting. The first considers the use of TXA across a variety of surgical settings,[18] and the second focuses on the use of antifibrinolytic agents in orthopedic surgery,[19] the main driver of perioperative blood transfusion in developed countries. Taken together, these analyses indicate that TXA decreases the risk of being transfused after surgery by a third, without significant differences in mortality or thrombotic events such as stroke, deep venous thrombosis (DVT), pulmonary embolism (PE), or myocardial infarction. In contrast, ε-aminocaproic acid did not reduce the number of patients transfused.[16,19]

Recombinant Activated Factor VII, Prothrombin Complex Concentrates, and Fibrinogen Concentrate

The "off-label" use of recombinant activated factor VII (rFVIIa) has been extensively assessed by randomized control trials as well as cohort and observational studies, and no survival benefit was found in the trauma setting.[20–22] Prothrombin complex concentrates and fibrinogen concentrate have not been evaluated for the treatment of bleeding trauma patients in randomized trials.[23] Although fibrinogen concentrate may eventually prove safe and effective in this setting,[24] extreme caution should be exercised in off-label use of prothrombin complex concentrate because these products may predispose to thrombosis.[25]

What Are the Available Data Concerning the Efficacy of TXA?

Data From the Surgical Setting

In 2012, a meta-analysis of surgical trials involving TXA identified 129 trials that included 10,488 patients.[18] Most of these trials were performed in elective surgery, the majority in cardiac surgery. Blood transfusion was evaluable in 95 trials (7,838 patients), and the risk of transfusion was reduced by 38% in the TXA group (pooled risk ratio, 0.62; 95% confidence interval [CI], 0.58–0.65; $p < 0.001$). The result remained unchanged when restricting the analysis to trials with adequate allocation concealment (32 trials, 3,408 patients; pooled risk ratio, 0.68; 96% CI, 0.62–0.74; $p < 0.001$) (Table 1) or to the trials with adequate blinding (69 trials, 5,968 patients; pooled risk ratio, 0.63; 95% CI, 0.59–0.68; $p < 0.001$).

In 2014, a retrospective analysis of 872 416 patients who underwent total hip or knee arthroplasty during a 6-year period in 510 US hospitals showed that transfusions needs for the 20,051 patients who received TXA were halved.[27] These results remained unchanged after multivariate analysis and propensity score matching.

Data From the Trauma Setting

TXA was studied in a large placebo-controlled double-blind randomized trial including 20,211 trauma patients

TABLE 1. Summary of Findings Concerning the Use of TXA in the Surgical Setting

Outcomes (Trials With Zero Events in Both Arms Were Omitted.)	Illustrative Comparative Risks* (95% CI)		Relative Effect (95% CI)	No. Participants (No. Events TXA/Control)	Quality of the Evidence (GRADE)
	Assumed Risk	Corresponding Risk			
	Control	Tranexamic Acid			
Risk of blood transfusion (32 studies)	369 per 1,000	251 per 1,000 (229 to 273)	RR, 0.68 (0.62–0.74)	3408 (459/509)	++++ high
Myocardial infarction (27 studies)	17 per 1,000	11 per 1,000 (7–18)	RR, 0.68 (0.43–1.09)	3173 (16/25)	+−−− very low**†‡
Death (28 studies)	9 per 1,000	6 per 1,000 (4–9)	RR, 0.61 (0.38–0.98)	3186 (9/15)	++−− low§
Stroke (16 studies)	17 per 1,000	22 per 1,000 (not estimable)	Not estimable	1996 (23/16)	++−− low‡¶
Deep vein thrombosis (19 studies)	37 per 1,000	32 per 1,000 (not estimable)	Not estimable	1572 (25/29)	+++− moderate‡¶
PE (10 studies)	19 per 1,000	9 per 1,000 (not estimable)	Not estimable	878 (4/8)	++−− low‡¶

*The basis for the assumed risk (e.g., the median control group risk across studies) is provided in the footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

**The assessment of myocardial infarction was not homogenous between studies. No systematic detection policy was used except the study of Zufferey et al.[26]

†Grouped analysis showed conflicting results.

‡Because of the lack of systematic detection, the number of detected events was very low, and so the CI is wide.

§The number of detected events was very low, and so the CI is wide.

¶Because of the small number of events, the CI is wide.

Data are from the meta-analysis of Ker et al. (2012).[17]

GRADE Working Group grades of evidence:

High quality: further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: we are very uncertain about the estimate.

RR, risk ratio.

recruited in 274 hospitals in 40 countries: CRASH-2 [Clinical Randomization of an Antifibrinolytic in Significant Hemorrhage, published in 2010].[28] This study showed that administration of 1 g of TXA over 10 minutes followed by 1 g over 8 hours reduced significantly overall mortality (14.5% vs. 16%) without any increase in thrombotic events. CRASH-2 was built on a realistic design aimed at including a large spectrum of trauma severity with the goal of reducing bleeding; most patients were enrolled in low-income countries. There was an absolute risk reduction of 15 fewer deaths per 1,000 patients treated (number needed to treat 67), but a post hoc analysis revealed that when TXA was given within 1 hour after trauma, mortality caused by bleeding was reduced by one third. When given between 1 hour and 3 hours after trauma, mortality was reduced by one fifth. By contrast, when given beyond the third hour, TXA seemed to increase mortality caused by bleeding by more than 40%.[29] Further analysis of the mortality of the entire cohort according to the severity of trauma assessed by the probability of death showed an equal relative benefit for each stratum of baseline risk.[30] The reduction in blood loss associated with TXA use in the elective surgical setting was not observed in this trial, which showed no difference between the two groups in transfusion rate, need for surgery, and amount of blood products transfused. Several concerns with study design and data gathering must be discussed. First, very few patients came from countries where trauma care included the full state-of-the-art of trauma resuscitation, especially early availability of blood products. Second, blood losses and data concerning severity of injury were not clearly reported. Third, there was no systematic adverse event reporting. Nonetheless, CRASH 2 remains one of the largest, placebo-controlled double-blind randomized trials performed in trauma and the largest to address the benefit of TXA.[31]

Data concerning the use of TXA in war surgery are available from the MATTERs I and MATTERs II studies. MATTERs I was a retrospective analysis of 896 casualties who received at least 1 U of packed red blood cells (PRBCs) from January 2009 to December 2010 in the Role 3 medical treatment facility of Camp Bastion in southern Afghanistan.[32] The goal of the study was to analyze the impact of TXA (n = 293) on survival at 30 days or hospital discharge. Mortality was 17.4% for patients receiving TXA and 23.9% for patients not receiving TXA in the overall cohort, and 14.4% and 28.1%, respectively, for those needing a massive transfusion. After multivariate analysis, the survival benefit of TXA remained statistically significant for patients needing a massive transfusion (odds ratio [OR], 7.2; 95% CI, 3–17.3). For the entire cohort, the factors significantly associated with death were Glasgow Coma Scale (GCS) score of 8 or less, hypotension, and coagulopathy. These results suggest a survival benefit with the use of TXA but do not prove it because of the retrospective design of the study. In addition, even though the two groups received the same PRBC/fresh frozen plasma ratio, including patients receiving a massive transfusion, cryoprecipitate was used more in the TXA massive transfusion group. The assessment of this confounding factor was the rationale for the MATTERs II study, which included 1,332 patients requiring at least 1 U of PRBCs from March 2006 to March 2011 at the same Role 3 medical treatment facility.[33] The goal of the study was to assess the respective roles of TXA and cryoprecipitate by comparing the outcome of four groups of patients: TXA only, cryoprecipitate only, both TXA and cryoprecipitate, or neither product. The authors used propensity scoring to adjust for most significant predictors of outcome including transfusion requirements and PRBC/fresh frozen plasma ratio but not platelet or rFVIIa use. The result was a similar, additive, but not synergistic, association with a reduction in mortality with the use of TXA and cryoprecipitate (both having an OR of 0.61 for mortality, 95% CI of 0.42–0.89 and 0.40–0.94, respectively). After adjustment for platelet administration, the ORs were 0.62 (95% CI, 0.43–0.90) and 0.59 (95% CI, 0.39–0.91), respectively. The administration of both products in combination was associated with an OR of 0.34 (95% CI, 0.20–0.58), which remained unchanged after adjustment for platelets. The confounding effect of heterogeneous rFVIIa use (30.4% in the cryoprecipitate-only group, 19.4% in the TXA/cryoprecipitate group, 3.4% in the TXA-only group, and 4% in the group receiving neither TXA nor cryoprecipitate) represents an important limitation to the interpretation of the study's results.

A small study in civilian trauma did not observe a mortality benefit in patients treated with TXA at physician discretion.[34] This retrospective study compared 150 patients treated with TXA and 150 control patients matched using a propensity score based on age, sex, traumatic brain injury, mechanism of injury, systolic blood pressure, transfusion requirements, and Injury Severity Score (ISS). Mortality was higher in the TXA group. The choice of elements included in the propensity score was not explained, and more surprisingly, the control group had lower transfusion requirements and a longer time to operative intervention, suggesting that the propensity score failed to account for important variables, resulting in a control cohort that was less severely injured than the TXA group. Further limiting interpretation of this study, no multivariate analysis was performed. Another study conducted in a civilian trauma center, a prospective cohort study, included 385 adult, severe trauma (ISS > 15) patients recruited over 2 years. Of these, 160 received TXA and 225 patients did not. Patients receiving TXA had higher ISS, incidence of shock (base deficit > 6 mEq/L), and transfusion requirements. Despite higher injury severity in the TXA group, no significant differences in mortality or multiorgan failure (MOF) were detected between groups (mortality, 8% vs. 8%; MOF, 30% vs. 37%). Multivariate analysis demonstrated a statistically significant reduction in mortality and MOF for patients treated with TXA in the subgroup of patients with shock (OR for mortality, 0.16 [95% CI, 0.31–0.86]; OR for MOF, 0.27 [95% CI, 0.1–0.73]). A similar trend was demonstrated for the entire study population; however, it did not reach statistical significance.[35]

What Are the Available Data Concerning the Safety of TXA?

Data From the Surgical Setting

Safety data from the surgical setting are scarce because of the low number of adverse events recorded in randomized trials (Table 1). A recruitment bias is highly possible because of the exclusion from randomized control trials of patients with known thrombotic risk. A recent meta-analysis concludes that the effect of TXA on risks of vascular occlusive events is uncertain.[18] Despite its large size, the cohort study (872,416

patients) by Poeran et al.[27] does not add much information because of very low incidence in reported thrombotic events (0.4% vs. 0.5 in the TXA vs. the non-TXA groups, no statistically significant difference after multivariate analysis or propensity score matching).

Nonetheless, the preponderance of studies in cardiac surgery allows some insight about the low arterial thrombosis risk associated with TXA.[36] Likewise, studies in orthopedic surgery provide an interesting insight on the low venous thrombotic risk associated with TXA.

Zufferey et al.[19] analyzed 18 trials comparing TXA versus placebo in orthopedics. In the five double-blind randomized trials that systematically screened for DVT using an objective test, the adjusted pooled incidences of DVT were 20.8% versus 20.9% for TXA and placebo, respectively. The results were not different in open-label studies or studies that only evaluated for DVT when patients were symptomatic (heterogeneity test between open and double-blind subgroups was $p = 0.61$). Thus, the data were pooled, and the estimated risk of DVT did not reveal statistically significant differences between TXA and placebo.

Data From the Medical Setting

TXA is widely used for the medical treatment of menorrhagia, and case-controlled studies show no association with an increased risk of venous thromboembolism (VTE).[37,38] Antifibrinolytics have been used occasionally in other settings, such as the management of bleeding risk or hemorrhage in patients with hematologic malignancies, but experience and safety data are limited.[39,40]

Data From the Trauma Setting

As expected, most of the data come from CRASH-2, which captured only clinically significant vascular occlusive events. There was no significant difference in stroke, DVT, and PE between the TXA and placebo groups; the rate of myocardial infarction was significantly lower in the TXA group. The rate of vascular occlusive events was low (1.7% for TXA vs. 2.0% for placebo), leading to wide CIs, and the authors conclude that they "cannot exclude the possibility of some increase in risk."[28] Concerning the war setting, the MATTERs I study observed a higher rate of VTE for patients receiving TXA,[32] but the difference did not persist after multivariate analysis, and the authors attributed this phenomenon to the burden of injury, which has a well-established relationship with the frequency of DVT.[26,41–43] No data concerning the rate of thrombotic events are available from the MATTERs II study.

What Are the Available Data Concerning the Use of TXA in the Prehospital Setting?

Since 2010, British Army medical emergency response teams have used TXA.[44] The same policy has been implemented by the NHS ambulance service in the United Kingdom since July 2011. A civilian air ambulance (Bergen, Norway) has used TXA since 2011 and added freeze-dried plasma (LyoPlas N–w, Deutsches Rotes Kreuz, Blutspendedienst West, Hagen, Germany) in 2013. Recently (2014), this approach was augmented with 2 U of freshly produced RBCs stored in a "golden hour box" as a damage-control resuscitation "bundle of care" immediately available for hemorrhaging patients on scene. Supplying the prehospital chain with fresh RBCs stored for less than 8 days is less likely to cause wastage and also provides hemorrhaging patients fresh RBCs with minimal "storage lesion." Preliminary results show that freeze dried plasma was used in 16 patients with severe hemorrhage in the first 12 months, before RBC introduction. Including trauma (n = 9) and nontrauma patients (n = 7), the majority (75 %) received TXA on scene. No adverse events were recorded. In Israel, TXA has been used by Israeli Defence Forces (IDF) since 2011 and the national EMS system since 2012. TXA is a cornerstone of military prehospital care in the IDF, along with freeze-dried plasma, both administered at the point of injury.[12] The IDF reported its experience regarding the first 40 casualties treated, for whom TXA was administered early (82% in <1 hour after injury and always in <2 hours). In this small cohort, no VTE events attributable to TXA were identified.[45] A follow-up report summarized the combined experience of the IDF and the civilian national EMS in Israel. This report demonstrated high adherence to clinical practice guidelines and no adverse reactions attributable to TXA. In two patients, thromboembolic events were recorded; however, both patients experienced injuries associated with a strong predisposition toward thromboembolism. TXA was also used extensively by the IDF on the Israeli-Syrian border where humanitarian medical care is provided to Syrian patients of the ongoing civil war. In a series describing the care provided to 258 Syrian casualties, 30% of the patients received TXA in the prehospital setting. Because the series included only prehospital data, late complications of the drug cannot be assessed. No early complications were reported for these patients.[46] Another report on a small cohort of patients who received TXA during aeromedical evacuation in Canada indicated that TXA use did not result in any detectable complications.[47] In the French Army, the use of TXA was implemented in 2011; currently, 100% of patients needing an emergency transfusion of plasma (i.e., indicative of the need for massive transfusion) receive TXA. The product is used in the prehospital setting along with French lyophilized plasma. This concept of RDCR was implemented in MEDEVAC teams and French Special Forces in remote places in Africa in 2011. Since that date, the "Centre de Transfusion Sanguine des Armées" (CTSA) ensures traceability of this practice. From 2011 to 2013, 113 transfusion episodes concerning 54 patients were traced with a growing proportion of patients receiving TXA during RDCR (3-year average, 20.3%). Fibrinogen was also given to 6 of 54 patients, and no unexpected adverse effects were reported. Recently, the use of TXA in the prehospital setting was approved by the US Department of Defense.

CONCLUSION

There exists a large body of data documenting the hemostatic efficacy and safety of TXA across a wide range of surgical settings. CRASH-2 demonstrated a survival benefit from the use of TXA within the first 3 hours after trauma. Returning to the questions posed in the introduction, we conclude the following:

1. Currently, we have no better pharmacologic options than TXA for prehospital hemostatic interventions.

2. High-quality evidence demonstrates the efficacy of TXA in reducing bleeding in elective surgery and reducing mortality in trauma. Reduction in mortality was observed for a wide range of trauma severities. When given within the first hour following injury, TXA reduced deaths from hemorrhage by one third. Prehospital use of TXA is the best way to assure that it is given within the first hour.
3. Decades of use since the 1960s and hundreds of clinical trials in surgery suggest low risks of adverse effects.
4. Data concerning TXA prehospital use are scarce, but recent military and civilian experience in several countries demonstrates its feasibility.

Despite these encouraging findings, work remains to be done. First, efforts to gather data concerning TXA effects on trauma patient outcomes must continue. Several clinical trials funded by the US Department of Defense as well as the PATCH trial in Australia and New Zealand will undoubtedly refine our understanding of TXA effects on coagulation, blood loss, transfusions, and clinical outcomes.[48–50] Second, implementation into clinical practice represents a challenge in medical education. Third, the importance of monitoring adverse effects must not be underestimated since the high incidence of VTE in trauma, regardless of TXA use, will continue to raise concerns. The implementation of trauma registries in organizations using TXA will provide data on this new and specific indication. Fourth, the use of TXA in the prehospital setting must not be considered alone but included in a bundle of care including blood products as in the French and Israeli militaries, which combine its use with the transfusion of freeze-dried plasma, or as in the United Kingdom where it is combined with RBC and fibrinogen transfusion. As suggested by the MATTERs II study, this approach may have additive survival benefits.

Damage-control resuscitation is the cornerstone of care for hemorrhaging patients. Efforts to assimilate these concepts into prehospital care should continue.

AUTHORSHIP

S.A., E.G., G.S., R.N., A.P.C., and A.S. contributed in gathering bibliography, writing, and editing the manuscript. C.H., R.N., G.S., and S.P. gathered data concerning the prehospital use of TXA.

DISCLOSURE

The authors declare no conflicts of interest.

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