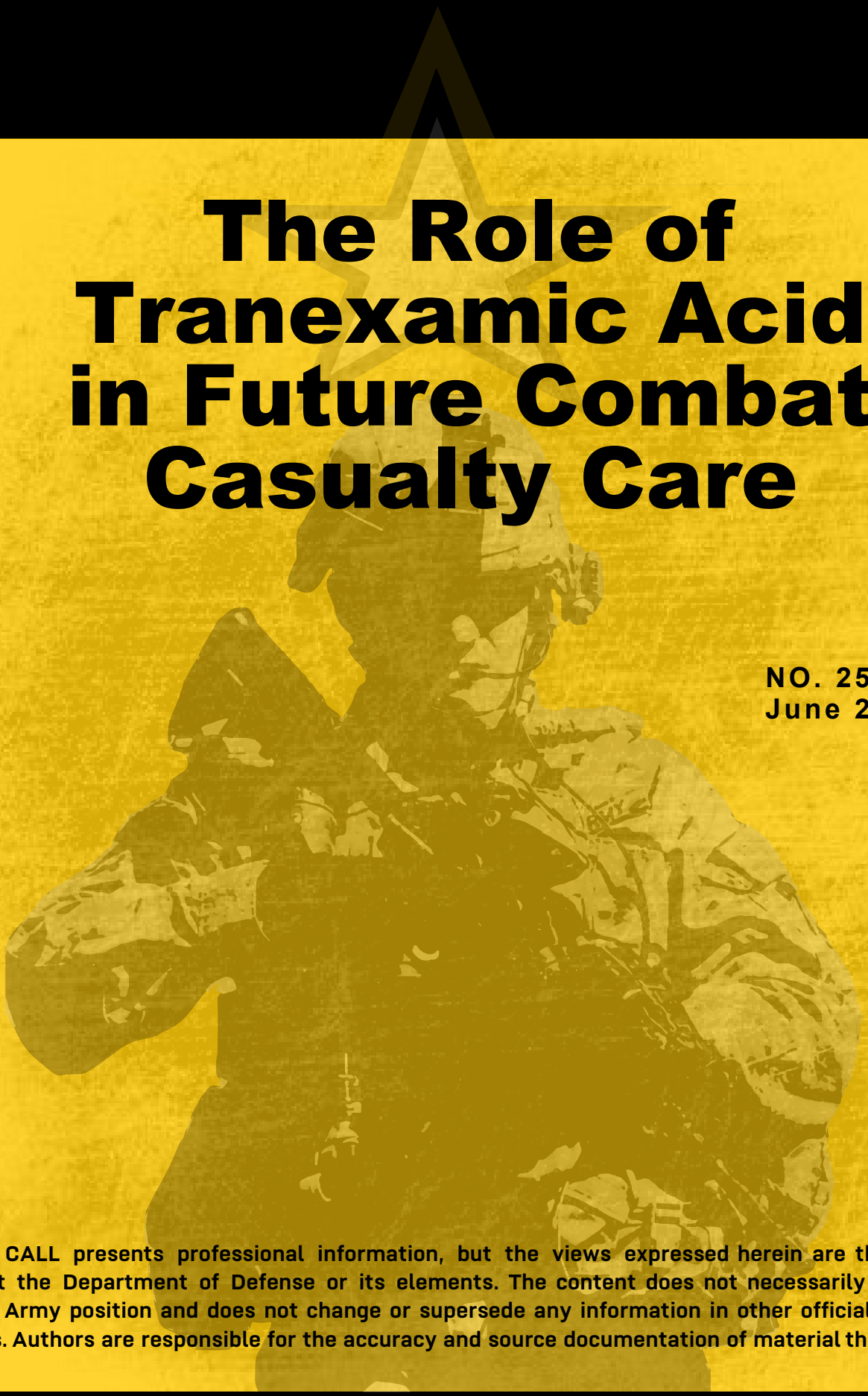
The Role of Tranexamic Acid in Future Combat Casualty Care



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EXECUTIVE SUMMARY

This paper is geared toward the Department of Defense medical community, in particular, the U.S. Army Medical Command (USAMEDCOM), and advocates for the widespread adoption of tranexamic acid (TXA) across all levels of military medical care to significantly reduce trauma-related mortality. Evidence from civilian trials (Clinical Randomization of an Antifibrinolytic in Significant Haemorrhage-2 [CRASH-2]), military studies (Military Application of Tranexamic Acid in Trauma Emergency Resuscitation [MATTERS]), the recent experience in the Russia-Ukraine War, and the subsequent Clinical Randomization of Tranexamic Acid to Improve Survival in Trauma (CRITICAL) study demonstrates TXA's effectiveness in controlling hemorrhage and improving survival rates. Ukraine reports a 33-percent reduction in deaths. TXA is a cost-effective intervention (approximately $30 per dose), particularly crucial in scenarios with prolonged prehospital care, such as anticipated future large-scale combat operations (LSCO). The paper recommends USAMEDCOM prioritize TXA implementation, including collaboration with international partners to develop and deploy a TXA auto-injector for rapid administration in the field. Expanding TXA access is a vital step toward enhancing battlefield survivability and improving patient outcomes, especially within the LSCO environment.

OBSERVATION

The use of TXA, as evidenced by Ukraine's Armed Forces experience, has been shown to reduced mortality by 33 percent.[1]

DISCUSSION

Trauma is a leading cause of death and disability globally.[2] Hemorrhage remains the most common cause of preventable death, following traumatic injury. The conflict in Ukraine has resulted in a high incidence of severe trauma, including significant bleeding. TXA, a medication that reduces bleeding, has become a critical component of prehospital and hospital care for wounded Soldiers and civilians. The scale of need in Ukraine exceeds that of typical peacetime scenarios, presenting opportunities to save lives and challenges in implementation.

Tranexamic Acid Background

"Originally developed in the 1960s by Japanese researcher Utako Okamoto, TXA has gained global recognition and is included on the World Health Organization's list of essential medicines. It is available in tablet and injectable forms, with effects lasting approximately three hours"[3]

Tranexamic acid is a synthetic lysine amino acid compound used for various medical purposes, primarily "to treat or prevent excessive blood loss from major trauma, postpartum bleeding, surgery, tooth removal, nosebleeds, and heavy menstruation."[4] Once clots form, the body initiates a process of fibrinolysis, releasing tissue plasminogen activator (tPA)—the same medication administered intravenously as a clot-busting treatment for heart attacks and strokes. TXA works by inhibiting the body's enzymes from breaking down blood clots, stabilizing existing clots and reducing overall blood loss.

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[1] Reuters. *Ukraine's Use of Tranexamic Acid Cuts Soldier Deaths by a Third*. 2024. Accessed 22 April 2025.
[2] Rossiter, Nigel D. *Trauma—the forgotten pandemic?* National Library of Medicine. Accessed 18 June 2025. https://pmc.ncbi.nlm.nih.gov/articles/PMC8438546/.
[3] Kalso, Reed. *Tranexamic acid (TXA)*. 2023. EBSCOhost. Accessed 25 April 2025. https://www.ebsco.com/research-starters/health-and-medicine/tranexamic-acid-txa.
[4] British National Formulary (BNF). *Tranexamic Acid*. 2015.

Tranexamic Acid Chemical Structure

Tranexamic acid possesses a simple chemical structure, comprising a cyclohexane ring with an amino and a carboxylic acid group attached. See figure 1.

Synonym(s): trans-4-(aminomethyl) cyclohexane carboxylic acid, AMCA, AMCHA, HAKU, TAMCHA, TXA

Linear formula: H2NCH2C6H10CO2H

Molecular formula: C8H15NO2

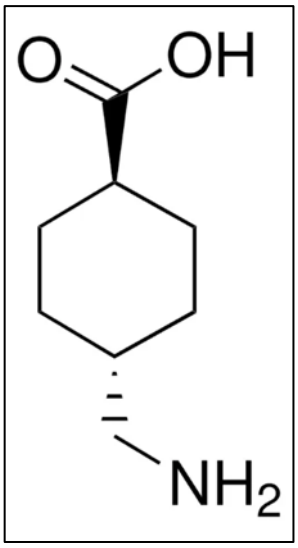

Figure 1. Tranexamic acid chemical structure[5]

Tranexamic Acid Administration Routes

TXA is typically administered intravenously (IV) in hospital and prehospital settings. Current IV recommendations for trauma-associated hemorrhage generally follow a loading dose of 1,000 milligrams administered over 10 minutes, followed by 1,000 milligrams infused over the subsequent 8 hours. These recommendations stem from the CRASH-2 clinical trial, which informs many current emergency medical services (EMS) protocols.[6] TXA is also available in oral form (tablets), commonly used for heavy menstrual bleeding and in the short-term prevention of bleeding in patients with hemophilia, including those undergoing tooth extractions or experiencing menorrhagia. Currently, intramuscular (IM) administration of TXA is not an approved method.

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[5] "Tranexamic Acid." ChemSpider. Accessed 22 April 2025. https://www.chemspider.com/Chemical-Structure.10482000.html.

[6] Bivens, Matt. MD. *Is TXA a Lifesaving Drug That's Too Cheap to Bother Using?* JEMS: Emergency Medical Services. 21 November 2024. Accessed June 1, 2025. https://www.jems.com/patient-care/emergency-medical-care/is-txa-a-lifesaving-drug-that-s-too-cheap-to-bother-using/.

Cost

TXA is a relatively inexpensive medication, with Massachusetts' EMS estimating the cost at $30 per dose.[7] Its affordability makes it an effective intervention for controlling hemorrhage in modern battlefield trauma.[8] Compared to TXA with current prices of $30 per 1g dose (converted to milliliter [mL], which equates to 1.0 mL of TXA) to Qfitlia (fitusiran), a drug used to treat hemophilia, which has an average price of $68,929 for a supply of just 0.2 mL, TXA is cost effective.[9]

TXA in Civilian Use and Studies

Civilian use of TXA in controlling trauma-related hemorrhaging is well documented. The CRASH-2 trial, conducted by the London School of Hygiene & Tropical Medicine, is a landmark study. More than 40 countries and 286 hospitals participated in the research. The CRASH-2 trial demonstrated a statistically significant reduction in mortality with TXA:

- Overall mortality: 14 percent in the TXA group versus 16 percent in the placebo group (relative risk 0.87, 95 percent confidence interval 0.76–0.99). TXA reduced the risk of death by 13 percent compared to the placebo.
- Death due to bleeding: TXA significantly reduced death specifically due to hemorrhage (relative risk 0.80, 95 percent confidence interval 0.64–0.99).
- Blood transfusion: Patients receiving TXA were less likely to require blood transfusions.
- Surgery: No significant difference was observed in the need for surgical interventions.
- Adverse events: No statistically significant increase in thromboembolic events (e.g., deep vein thrombosis, pulmonary embolism) was noted in the TXA group. This finding was crucial, as concerns about increased clotting risks were a potential drawback of antifibrinolytic therapy. A small numerical increase in events was observed, but it did not reach statistical significance.[10]

[7] Ibid.
[8] Ibid.
[9] "Qfitlia Price Guide." Drugs.com. Accessed 21 May 2025, https://www.drugs.com/price-guide/qfitlia.
[10] CRASH-2 Trial Collaborators. *Effect of Tranexamic Acid on Death, Vascular Events, and Transfusions in Trauma Patients with Significant Bleeding*. The Lancet 376, no. 9747 (2010): 1645–58.

The CRASH-2 report demonstrates the analysis of data from 40,000 trauma patients and women with severe bleeding after childbirth, illustrating the impact of treatment delay in TXA administration. See figure 2.

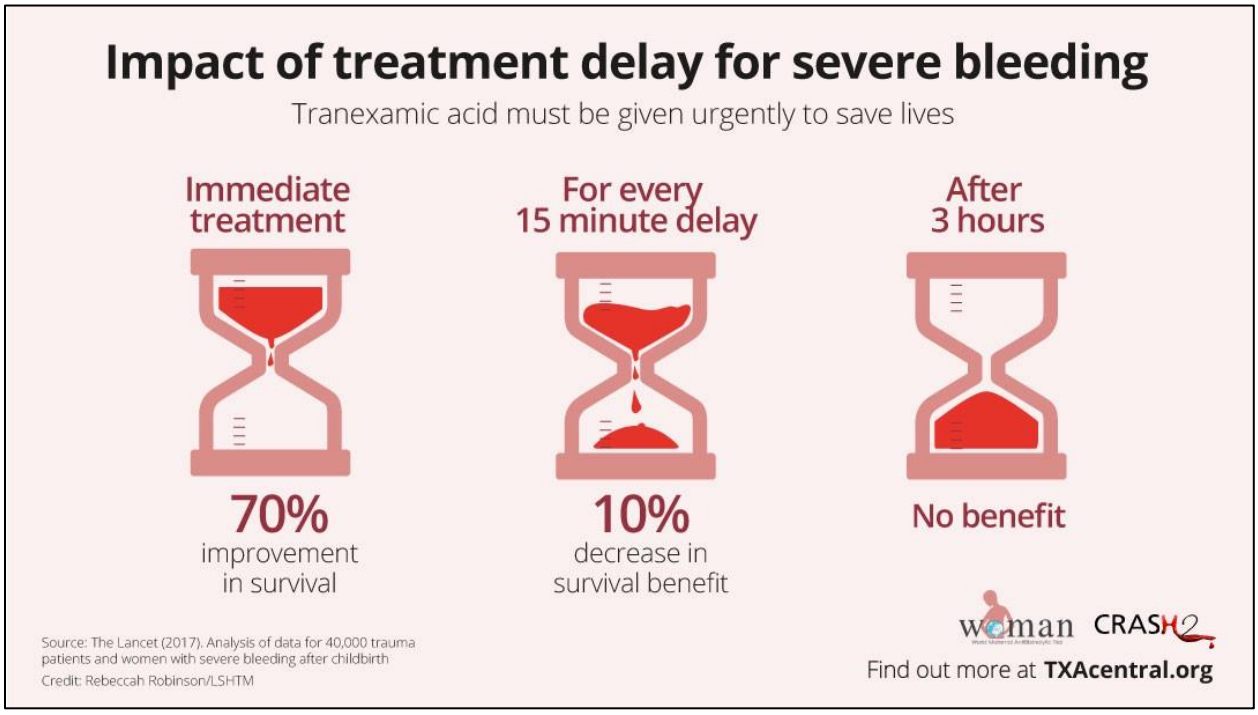

Figure 2. CRASH-2 report analysis further demonstrates that for every 15-minute treatment delay in trauma patients and women with severe bleeding after childbirth, there is a 10 percent decrease in survival benefit.

Military Application of Tranexamic Acid and Studies

The MATTERS study, published in 2012, aimed "to characterize contemporary use of TXA in combat injury and to assess the effect of its administration on total blood product use, thromboembolic complications, and mortality."[11] This study was conducted at a role 3 echelon surgical hospital, Camp Bastion, in southern Afghanistan. Approval for this study was obtained through the UK Joint Medical Command Research Pillar and the U.S. Army's Medical Research and Materiel Command, and data was collected from 1 January 2009 through 31 December 2010.

The MATTERS trial addressed challenges unique to military trauma: remote locations, prolonged prehospital times, explosive injuries, and limited resources. The study aimed to determine if early TXA administration by combat medics could reduce mortality in injured military personnel.

The MATTERS trial concluded that, "The use of TXA with blood component-based resuscitation following combat injury results in improved measures of coagulopathy and survival, a benefit that is most prominent in patients requiring massive transfusion. Treatment with TXA should be

[11] Eastridge, Bryan J., et al. *Tranexamic Acid for Trauma: A Consensus-Based Guideline from the Eastern Association for the Surgery of Trauma*. Journal of Trauma and Acute Care Surgery 85, no. 1 (July 2018): 133–47.

implemented into clinical practice as part of a resuscitation strategy following severe wartime injury and hemorrhage."[12]

The MATTERS trial showed—

- 24-hour mortality: 18.2 percent in the TXA group versus 24.6 percent in the placebo group (odds ratio 0.70, 95 percent confidence interval 0.52–0.94), representing a 31 percent reduction in the odds of death within 24 hours.
- 30-day mortality: A trend toward reduced mortality at 30 days in the TXA group, although not statistically significant.
- Transfusion requirements: Patients receiving TXA were less likely to require blood transfusions.
- Adverse events: No significant increase in adverse events, such as thromboembolic complications, was observed in the TXA group.

The Journal of the American Medical Association (JAMA) noted that this was the first study to examine TXA effectiveness in managing wartime injury.[13]

The findings confirm those of the CRASH-2 trial and extend them to a population of patients with wartime injuries.[14]

Tranexamic Acid and the Feasibility of an Auto-Injector for Military Use

COL Chris Wright, the former chief medical officer for the Royal Army Medical Corps (2022-2023), has been a strong advocate for a TXA auto-injector since the mid-2000s. Currently serving in the AH Medical Operations and Commitments within the UK Ministry of Defense (MOD), Wright brings extensive experience to this issue, including more than 12 tours in Iraq and Afghanistan, a role as British liaison officer for the U.S. Defense Health Agency (2019-2022), and positions at the Defense Academy of the United Kingdom.[15]

As early as 2013, COL Wright proposed the feasibility of battlefield TXA administration via an auto-injector. Wright's paper, *Battlefield administration of TXA by combat troops: a feasibility analysis* suggested incorporating 1g of TXA into an intramuscular auto-injector for self- or buddy-administration following severe injury.[16]

COL Wright argued TXA "is safe and effective, and it would take little effort to repackage it as an auto-injector and issue to all personnel at risk, along with their dressings and tourniquets."[17]

Auto-injectors are, by design, easy to use and suitable for self-administration by patients, administration by untrained personnel, or efficient use by healthcare professionals. Existing auto-

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[12] Ibid.
[13] Ibid.
[14] Shakur, H., et al. *Effect of Tranexamic Acid on Death, Vascular Events, and Transfusions in Trauma Patients with Significant Bleeding*. The Lancet 376, no. 9747 (2010): 1645–58.
[15] RocketReach. *Chris Wright*. Accessed 21 May 2025. https://rocketreach.co/chris-wright-email_286712026.
[16] Wright, C. *Battlefield administration of tranexamic acid by combat troops: a feasibility analysis.* Journal of the Royal Army Medical Corps. *161*(6), 428–434. Downloaded 26 September 2014. Sent to author via email 8 April 2025. https://jramc.bmj.com/.
[17] Ibid.

injectors containing atropine and 2-PAM-CI (pralidoxime chloride) are standard components of the Mark I nerve agent antidote kit (NAAK). As COL Wright explained in a 2019 article in The Daily Telegraph, "You cannot train all Soldiers to do intravenous administration, so it was an obvious idea to put it into an auto-injector so everyone can carry it and administer it when they need to."[18]

The ongoing conflict in the Russia-Ukraine War highlights the increasing challenges of rapid medical evacuation. Quick evacuations within one hour are no longer consistently achievable, with medical evacuation times from the forward line of own troops (FLOT) often extending to multiple hours, or even days. Ukrainian forces are already using TXA to reduce mortality from hemorrhaging by 33 percent. Given these realities, a self-administered, dose-ready package for controlling battlefield-induced hemorrhage is a logical and potentially life-saving advancement.

Furthermore, this innovation has clear potential beyond the battlefield. Like other military medical breakthroughs, a TXA auto-injector could be readily adapted for civilian applications, benefiting first responders and potentially saving countless lives in situations, such as traffic accidents and worksite trauma. The UK is leading this development, with a £5 million investment announced in The Daily Telegraph in 2019, with the expectation that the technology will have "an immediate impact in terms of reducing the number of deaths on the battlefield."[19]

Tranexamic Acid Use in the Russia-Ukraine War and Studies

Following the Russian invasion, Ukraine became one of the first nations to adopt widespread prehospital TXA administration as a standard of care for combat-related trauma. This was driven by the experience of military doctors and the urgent need to address battlefield trauma. The scale of TXA use in Ukraine is unprecedented. Ukraine adopted TXA as a standard treatment for battlefield injuries early in the war, recognizing the high risk of blood loss from shrapnel and blast injuries.[20]

This widespread use prompted a study by the University of Birmingham, UK. The CRITICAL study, led by Professor Ian Greaves, involved 24 hospitals in Ukraine and enrolled more than 12,000 severely injured patients with suspected hemorrhage.[21]

The CRITICAL study aimed to determine whether TXA administration improved survival beyond three hours after injury. It found a significant reduction in 28-day mortality in the TXA group compared to the placebo group, reducing the risk of death by approximately 18 percent. This was consistent across different injury patterns and time windows (up to 12 hours).[22]

Ukrainian protocols recommend early TXA administration for almost all significant trauma cases, including penetrating and blunt trauma, typically 1g IV, with a second gram if bleeding continues.[23]

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[18] The Daily Telegraph. *Soldiers to Get New Blood-Clotting Technology to Save Lives on the Battlefield*. 16 April 2019.
[19] Ibid.
[20] Reuters. *Ukraine's Use of Tranexamic Acid Cuts Soldier Deaths by a Third*. 2024. Accessed 22 April 2025.
[21] Zacharias, C.R., et al. 2024. *Clinical Randomization of Tranexamic Acid in Critical Hemorrhage (CRITICAL) study: a randomized, placebo-controlled, double-blind trial*. The Lancet 403 (10431): 999–1010.
[22] Ibid.
[23] Ibid.

Lessons Learned from the Russia-Ukraine War

The CRITICAL study yielded three key takeaways:

- Revision of TCCC guidelines: The three-hour window for TXA administration has been removed. The recommendation is to administer TXA as soon as possible after injury if hemorrhage is suspected.[24]
- Wider adoption of TXA: The CRITICAL study is expected to lead to wider adoption of TXA in military and civilian trauma care.
- Potential for prehospital auto-injectors: Like tourniquets, a TXA auto-injector could feasibly be included in the next generation of individual first aid kits (IFAKs) to assist hemorrhage control.

Tranexamic Acid Use in Future Large-Scale Combat Operations

Future LSCO are expected to increase the scope of combat-induced trauma to levels not seen since World War II and the Korean War. Furthermore, potential limitations in air superiority may restrict evacuation, extending the "golden hour." Extended time to advanced surgical support, particularly within the U.S. Indo-Pacific Command (USINDOPACOM) area of responsibility (AOR), will necessitate far-forward care, including treatment of hemorrhaging injuries with medications like TXA outside of a hospital setting.

RECOMMENDATIONS

The modern operating environment demands a resilient and adaptable USAMEDCOM. Facing the prospect of great power competition, multi-domain operations, and evolving threats, USAMEDCOM must proactively enhance its readiness, embrace technological innovation, and prioritize personnel well-being. USAMEDCOM should incorporate TXA into trauma care across all echelons, not just within special operations. USAMEDCOM should collaborate with the UK's MOD Defense Medical Services (DMS) and other interested NATO partners to facilitate the development and manufacturing of a TXA auto-injector, conduct clinical trials, and obtain Food and Drug Administration (FDA) approval for use no later than the fourth quarter of 2026. A TXA auto-injector should become as common as a tourniquet within the IFAK or the chemical biological defense (CBD) auto-injector. Within the doctrine, organization, training, materiel, leadership and education, personnel, facilities, and policy (DOTMLPF-P) framework, the incorporation of TXA into USAMEDCOM falls under—

- Doctrine: Establishing how and when to use TXA.
- Training: Providing training for TXA administration outside of a hospital environment.
- Material: Developing a new TXA auto-injector.
- Policy: Revising medical protocols to allow TXA administration as close to the point of injury as possible.

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[24] Joint Trauma System. *Tactical Combat Casualty Care (TCCC) Guidelines*. U.S. Department of Defense. 25 January 2024. Retrieved from https://tccc.org.ua/en/guide/tccc-guidelines-2021-eng?keyword=tccc%20guidelines%202022%20pdf.

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