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TRANEXAMIC ACID IN POLISH PRE-HOSPITAL EMERGENCY MEDICINE AND THE COMPETENCIES OF MEDICAL RESCUE TEAMS

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ABSTRACT

INTRODUCTION: Medical rescue teams (MRTs) are the basic components of the Polish Emergency Medicine System (PEMS) that provide pre-hospital emergency medical services. However, despite the possibility for paramedics to use 47 drugs and many complicated medical procedures, tranexamic acid was not found there. Efficacy of pre-hospital emergency medical services could be improved by using tranexamic acid (TXA) in the management of traumatic hemorrhage and traumatic brain injury (TBI). The aim of this study was to demonstrate that the competencies of MRTs should be expanded and that Polish paramedics should be authorized to independently administer TXA to TBI patients.

MATERIAL AND METHODS: The main research method was an analysis of the literature, including studies focusing on TXA administration and the associated risks. The article was written in the last two years.

RESULTS: The study demonstrated that TXA contributes to the effective management of selected types of hemorrhage and TBI and that the risk of adverse effects associated with TXA administration is minimal.

CONCLUSIONS: The gathered evidence suggests that paramedics should be authorized to independently administer TXA in pre-hospital care to maximize the efficacy of emergency medical services provided to patients in the PEMS.

KEY WORDS: tranexamic acid; hemorrhage; system; ambulance

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INTRODUCTION

Tranexamic acid (TXA), an antifibrinolytic agent for bleeding control, has attracted considerable interest in recent years. Numerous clinical trials have been conducted to evaluate its efficacy and safety in emergency medicine, including WOMAN [1], CRASH-2 [2], CRASH-3 [3], MATTERs [4], HALT-IT [5]. The applicability and efficacy of TXA have been also widely debated in the Polish medical rescuer community. Although the drug has been known since the 1960s, it is not widely used in the pre-hospital environment. This is an important consideration, since according to Stępka et al. [6], hemorrhage can be responsible for 35% of deaths in pre-hospital care and for 40% of deaths in hospitalized patients within 24 h after admission. Such a high number of bleeding-related

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deaths indicates that effective solutions, protocols, and technologies for managing massive hemorrhages are needed.

The Polish Emergency Medicine System (PEMS) provides medical rescue services in life-threatening emergencies on the territory of the Republic of Poland. The system is composed of hospital emergency departments (HEDs) as well as air ambulances (AAs) and Medical Rescue Teams (MRTs) that provide pre-hospital emergency medical services [7]. According to *Statistics Poland*, there were 1581 MRTs in Poland in 2020, including 1238 general MRTs and 343 specialist MRTs [8]. The number of MRTs in Poland has increased in recent years, but the availability of specialist rescue units has declined. There were a total of 1492 MRTs, including 560 specialist rescue units, in 2016 [9], 1519 MRTs, including 490 specialist units, in 2017 [10], 1541 MRTs, including 413 specialist units, in 2018 [11], and 1577 MRTs, including 369 specialist units, in 2019 [12]. These data indicate that the number of specialist rescue units has decreased by 38.7% over a period of 6 years. General MRTs differ from specialist rescue units in that they do not have to be staffed by doctors. General MRTs are the core units responsible for pre-hospital emergency medical response in Poland. The disproportions between the number of general and specialist MRTs are deepened each year. General MRTs are staffed mostly by paramedics (who accounted for 84.6% of ambulance personnel in 2020) as well as by nurses (8.8%) [8]. The competencies and decision-making powers of medical rescue personnel are significantly limited by legal regulations. Tranexamic acid is one of the drugs that can be administered to trauma patients only by doctors [13].

MATERIAL AND METHODS

This study attempts to answer the following research questions: How effective is TXA in controlling hemorrhage? Should TXA be placed on the list of drugs that can be administered independently by paramedics? The following research hypotheses were formulated: Tranexamic acid is effective in controlling certain types of hemorrhage. Tranexamic acid should be placed on the list of drugs that can be administered independently by paramedics.

The main research method was a quantitative review of the literature and other documents. The following types of data were analyzed: research articles, recommendations and guidelines, source literature, summary of product characteristics (SmPC) for Exacyl, and legal regulations.

Characteristics of tranexamic acid

Tranexamic acid has attracted considerable interest in recent years. A large review study published in May 2020 reported on an increasing number of PubMed citations (589 in 2019) and clinical trials (432 at the time of writing) evaluating TXA [14].

Tranexamic acid is a synthetic lysine amino acid derivative. It exerts antifibrinolytic effects by blocking lysine binding sites on plasminogen and inhibiting the formation of fibrin-degrading plasmin. Tranexamic acid displaces plasminogen from the fibrin surface, and it may directly inhibit plasmin. At high concentrations, TXA exerts anti-inflammatory effects by inhibiting plasmin-mediated activation of the complement system, neutrophils, and monocytes [15].

Tranexamic acid stabilizes clots and it may increase the risk of thromboembolic events [15]. According to the SmPC of Exacyl, a medicinal product containing TXA that has been authorized for use in Poland, the incidence of thrombosis in patients administered the drug is unknown. Tranexamic acid should not be administered to patients with active thrombotic disorders [16]. An international trial involving 12,009 patients demonstrated that the incidence of venous thromboembolic events was twice higher in patients administered TXA (0.8%) than in the placebo group (0.4%). The incidence of arterial thromboembolic events (stroke, myocardial infarction) was similar in both groups [5]. In other studies, the incidence of adverse events did not differ significantly between TXA and placebo groups [1, 3, 17, 18].

For many years, the recommended loading dose of TXA was 1 g in 100 mL of injectable solution (usually saline solution) administered intravenously over 10 minutes. This dose is described in most studies on the use of TXA in emergency medicine (often followed by a 1 g infusion over 8 hours) [19]. The prescribed protocol is easy to remember because it adheres to the KISS principle (Keep it simple, stupid) — all numbers (1 g, 10 minutes and 100 mL) are composed of two digits, and each number is ten times higher than the preceding number. The KISS principle was introduced to simplify protocols and data that have to be remembered and applied in emergencies. However, the dosing strategy for TXA

has been recently revised under the latest update to the Tactical Combat Casualty Care (TCCC) guidelines. The dose of TXA was increased to 2 g and administered via slow intravenous or intraosseous route [20]. Intravenous administration of diluted TXA solution has received some criticism. According to Woroń [21], the use of TXA as a hemostatic agent in intravenous solutions is not effective because TXA undergoes hydrolysis when diluted. The cited author argued that TXA should be administered by slow intravenous injection without dilution. The recent guidelines of the European Resuscitation Council (ERC 2021) recommend a loading dose of 1 g administered intravenously within 10 minutes, followed by a 1 g infusion over 8 hours [22]. These guidelines do not clearly specify that TXA needs to be diluted. A 1 g bolus dose in 100 mL of saline solution is still encountered in the existing guidelines. The TXA dose recommended by Prehospital Trauma Life Support (PHTLS) is 1 g in 100 mL of 0.9% sodium chloride solution administered over 10 minutes [23].

The reviewed literature, in particular a study on the effects of delayed administration of antifibrinolytics (Gayet-Ageron et al. [17]), indicates that TXA should be administered as soon as possible after the onset of bleeding. The study demonstrated that delayed treatment decreases the survival benefit by 10% per every 15 minutes of delay until 3 h, after which there are no benefits. These findings suggest that TXA administration should not be delayed in bleeding patients [17].

Tranexamic acid is relatively cheap (the average cost per 1 g was estimated at $5.70 in the cited study), and its cost-effectiveness was assessed based on evidence from the CRASH-2 trial. The study analyzed bleeding trauma patients from Tanzania, India, and the United Kingdom, and it demonstrated that early administration of TXA can be highly cost-effective in low, middle, and high-income settings [24]. Tranexamic acid has numerous uses in surgical treatment, and it effectively reduces blood loss, mortality, and transfusion requirements [15]. However, this article focuses on emergency medicine, and the application of TXA in surgical patients will not be discussed.

Literature review

The efficacy of TXA in emergency medicine has been demonstrated by several important studies, including CRASH-2 and CRASH-3 trials. These studies relied on the results of the CRASH-1 trial which investigated the effect of corticosteroids on death and disability after head injury. The trial was organized by the London School of Hygiene & Tropical Medicine (LSHTM) in collaboration with medical centers around the world, and the results were used by numerous researchers to assess the efficacy of TXA in trauma patients [25]. In the CRASH-2 trial evaluating the effect of early TXA administration on death and transfusion requirements in bleeding trauma patients, the loading dose was 1 g administered intravenously over 10 minutes, followed by an infusion of 1 g over 8 hours. Tranexamic acid was administered to 10,060 patients, and 10,067 patients were allocated to receive a placebo. Tranexamic acid significantly reduced all-cause mortality as well as the risk of death due to bleeding (4.9% vs 5.7%). The study also revealed that hemostatic benefits were strongly correlated with the time of administration. Mortality was reduced from 7.7% to 5.3% when TXA was administered within 1 h after injury, and from 6.1% to 4.8% when the treatment was applied within 3 h. However, mortality was higher in the TXA group (4.4%) than in the placebo group (3.1%) when TXA was administered later than 3 h after injury. The study confirmed that TXA effectively reduces the risk of death due to bleeding when administered within 3 h after injury [2].

The CRASH-3 trial was undertaken to assess the effects of TXA in patients with traumatic brain injury (TBI). Tranexamic acid was administered to 6406 patients, and 6331 patients were allocated to receive a placebo. The risk of head injury-related death reached 18.5% in the TXA group vs 19.8% in the placebo group. In patients with a GCS score of 3 and bilateral unreactive pupils at baseline, the risk of head injury-related death was 12.5% in the TXA group and 14% in the placebo group. The study demonstrated that TXA was effective in TBI patients when administered within 3 hours after injury [3].

The results of both trials and the role of TXA in the management of traumatic hemorrhage and in patients with TBI have been recognized by International Trauma Life Support (ITLS). The current position of ITLS is that [26]:

— there is sufficient evidence to indicate that TXA can be safely and effectively used in adult patients with traumatic bleeding;
— the use of TXA in the management of acute traumatic hemorrhagic shock is supported by

ITLS within the framework of the existing medical oversight and protocols;
- TXA should be used in conjunction with initial resuscitation and external bleeding control. Early administration of TXA can be considered after airway stabilization, external bleeding control and initial volume resuscitation;
- TXA treatment should also be considered in early stages of resuscitation and transport. Recent research indicates that TXA is most effective when administered within 3 h after injury and can be harmful when administered after that time;
- there is sufficient evidence to demonstrate that TXA delivers the greatest hemostatic effects in patients with TBI if administered as soon as possible within 3 h after injury.

The application of TXA in combat injury was investigated in the MATTERs study. This retrospective observational study analyzed the effects of TXA treatment in the combat setting. Data for the study were obtained from a surgical hospital in southern Afghanistan. A total of 896 hospital admissions with combat injuries, including 293 patients who received TXA, were analyzed. Mortality was lower in the TXA group, even in patients who were more severely injured than those who did not receive TXA. The greatest benefit was observed in patients who received massive transfusions. In this group, TXA was also associated with higher survival and lower incidence of coagulopathy. The authors concluded that the use of TXA with blood component-based resuscitation improves survival after severe combat injury and hemorrhage [4]. According to TCCC guidelines, in patients requiring blood transfusion, 1 g of TXA in 100 mL of normal saline or lactated Ringer's solution should be administered as soon as possible, but not later than 3 h after injury [27]. The updated version of TCCC guidelines [28] states that TXA should be administered by intravenous infusion over 10 minutes and that a second infusion of TXA should begin after initial fluid resuscitation has been completed [28]. The 2020 update introduced more extensive changes to TCCC guidelines. At present, TXA treatment is recommended already when a casualty is anticipated to need a significant blood transfusion. Tranexamic acid is also indicated in unconscious patients, casualties with severe blunt force or blast injury, and patients with suspected TBI. The currently recommended dose of TXA is 2 g administered by slow intravenous infusion [20].

The efficacy of TXA in managing TBI was also evaluated in a meta-analysis of 6 randomized controlled trials. The study confirmed that TXA effectively reduced the risk of death in patients with TBI ($p = 0.004$) [18].

The use of TXA for managing hyperacute primary intracerebral hemorrhage was examined in the TICH-2 international trial. However, the study did not confirm the clinically significant effects of TXA treatment. The authors concluded that larger randomized trials were needed to confirm or refute clinically significant treatment effects [29].

The ULTRA trial investigated the effect of TXA treatment on the clinical outcome of patients with aneurysmal subarachnoid hemorrhage. The overall case fatality rate did not improve after 30 days, and it was determined at 27% in the TXT group and 24% in the placebo group at 6 months. The study demonstrated that ultra-early, short-term TXA treatment did not improve clinical outcomes at 6 months [30].

The effects of TXA on thromboembolic events in patients with gastrointestinal bleeding were analyzed in the HALT-IT trial [5]. Meta-analyses of previous smaller trials revealed that TXA could reduce the risk of death from gastrointestinal breeding. Tranexamic acid was administered to 5994 patients, and 6015 patients received a placebo. A loading TXA dose of 1 g was dissolved in 100 mL of 0.9% sodium chloride and administered by slow intravenous injection over 10 minutes. This was followed by a maintenance TXA dose of 3 g added to 1 L of isotonic intravenous solution and infused at 125 mg/h for 24 h. Death due to gastrointestinal bleeding occurred in 222 (3.7%) of patients in the TXA group and in 226 (3.8%) patients in the placebo group. Based on these results, the authors concluded that TXA should not be used for the treatment of gastrointestinal bleeding.

The effect of TXA administration on mortality in women with post-partum hemorrhage (PPH) was investigated in the WOMAN international trial coordinated by the LSHTM. A total of 20,060 women were randomly assigned to receive TXA. Death from PPH was reduced in women administered TXA (1.5%) relative to the placebo group (1.9%; $p = 0.045$). The risk of death was especially lower in women who received TXA within 3 h after giving birth (1.2% vs 1.7%; $p = 0.84$). However, the composite primary endpoint of death from all causes was not reduced by TXA treatment (5.3% in the TXA group vs 5.5% in the placebo group; $p = 0.65$) [1].

Several studies have shown that TXA reduces the incidence of PPH, decreases mean blood loss and induces only mild side effects [31–33]. A meta-analysis conducted in 2018 also revealed that TXA effectively reduces blood loss when administered prior to cesarean delivery [34].

The effectiveness of inhaled TXA for the treatment of hemoptysis was analyzed in a randomized controlled trial in 2018 [35]. Nebulized TXA was administered at a dose of 500 mg. The treatment significantly reduced expectorated blood volume, shortened the mean length of hospital stay, and decreased the number of patients who required invasive procedures such as interventional bronchoscopy or angiographic embolization to control bleeding. In addition, the hemoptysis recurrence rate was also reduced at the 1-year follow-up ($p = 0.009$). Inhaled TXA did not induce additional side effects.

Tranexamic acid is also used in epistaxis treatment. Epistaxis may occur in patients taking antiplatelet medications such as acetylsalicylic acid and suffering from other disorders that affect the coagulation cascade. Some nosebleeds may be difficult to control, and they can lead to hypovolemic shock in extreme cases. The efficacy of TXA for the treatment of epistaxis in patients taking antiplatelet drugs was examined in a randomized control trial. Patients received topical TXA at 500 mg in 5 mL. Within 10 minutes after treatment, bleeding was stopped in 73% of the patients in the TXA group vs 29% of the patients who received anterior nasal packing (ANP). Epistaxis treatment with topical TXA also reduced recurrent bleeding at 1 week and improved patient satisfaction in comparison with ANP [36].

The potential use of TXA in pediatric hemorrhagic trauma was explored by Beno et al. [37]. Based on the existing evidence that TXA can be effectively and safely used for hemorrhage treatment in adults, the authors concluded that the drug should be considered for use in trauma patients younger than 16. The administration of TXA to pediatric trauma patients was also examined in a combat setting. Pediatric trauma admissions to a NATO hospital in Camp Bastion, Afghanistan, between 2008 and 2012 were analyzed. Tranexamic acid was administered mainly to patients with severe abdominal injuries and metabolic acidosis. The treatment decreased mortality, and adverse safety- or medication-related complications were not identified [38]. According to revised ERC guidelines (2021), children requiring transfusions after severe trauma, including TBI, should receive TXA as soon as possible at a loading dose of 15–20 mg/kg, followed by an infusion of 2 mg/kg/h over 8 hours [39]. The administration of TXA to children had not been recommended by the ERC guidelines of 2015 [40].

RESULTS

The effectiveness of TXA treatment in bleeding control has been evaluated based on an extensive literature review. The results of randomized trials such as CRASH-2 and MATTERs indicate that TXA reduces trauma mortality caused by hemorrhage provided that it is administered as soon as possible, not later than 3 h after injury. The efficacy of TXA in managing PPH was demonstrated by the WOMAN trial. Tranexamic acid was also found to be effective in the treatment of epistaxis and hemoptysis. These disorders do not constitute traumatic injuries, but they can pose a challenge for medical personnel operating in both pre-hospital and hospital settings, and TXA can be highly useful in managing these conditions. However, TXA did not reduce mortality or the incidence of serious complications in patients with gastrointestinal bleeding (HALT-IT), aneurysmal subarachnoid hemorrhage (ULTRA) or hyperacute primary intracerebral hemorrhage (TICH-2).

There is substantial evidence to indicate that TXA is useful in pre-hospital care provided by emergency medical services (with the above exceptions). Tranexamic acid not only reduces hemorrhage. The CRASH-3 trial demonstrated that TXA can be also effectively administered to patients with TBI. Despite the fact that the results were less conclusive than the findings of the CRASH-2 trial, TXA is recommended for use in both military and civilian emergency medical care, and these guidelines should be respected. Tranexamic acid is generally safe, and it does not cause significant or frequent side effects. Dose regimes and administration methods are relatively simple and based on international guidelines. According to the authors, the list of contraindications for TXA is short and easy to remember. The discussed drug is also cheap and its early administration is cost-effective. The cost of 1 g of TXA was estimated at $5.70 (international dollars based on a study published in 2011).

DISCUSSION

The results of CRASH-3 [41] and WOMAN [42] trials and their interpretation have also attracted some criticism in the scientific community. Morgenstern [41] observed that "TXA is not a wonder drug", and the authors subscribe to this opinion. Despite evidence that TXA can substantially benefit trauma patients, it cannot be expected to work miracles in massive hemorrhages, and it can decrease mortality only in selected cases and under supportive conditions. Therefore, healthy skepticism is advocated until the efficacy of TXA treatment has been established beyond doubt in further research.

The hypothesis postulating that TXA undergoes hydrolysis and, consequently, loses its therapeutic efficacy when diluted seems doubtful. In the HALT-IT trial, both the loading dose and the maintenance dose were diluted. The study found that TXT did not reduce mortality from gastrointestinal bleeding, but a higher incidence of venous thromboembolic events in the treated group suggests that TXA prevented the dissolution of blood clots. Dilution could compromise the efficacy of TXA, but further research is needed to confirm this observation, especially since the hydrolysis hypothesis has not been validated in other studies. According to the authors, the influence of the administration method on the efficacy of TXA should be evaluated in a separate study. Tranexamic acid continues to attract significant interest, and such studies could be expected in the near future.

CONCLUSIONS

The results of the literature review indicate that Polish paramedics should be able to administer TXA independently in daily practice. Tranexamic acid reduces blood loss most effectively when administered as soon as possible after injury, preferably in pre-hospital care. The observed decrease in the number of specialist rescue units staffed by doctors leads to the conclusion that TXA should be placed on a list of drugs that can be administered independently by paramedics. The cited studies provide clear evidence for the efficacy of TXA treatment, and it can be postulated that current Polish regulations that prevent paramedics from administering TXA independently pose a risk for trauma patients and women in emergency labor. The scale of the associated risks, potential economic losses, and potential benefits associated with TXA administration by paramedics should be examined in the future. Further research could substantially contribute to the discussion on the role of TXA in Polish emergency medicine.

Conflict of interest

The authors have no conflict of interest to declare.

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