Journal Pre-proof

Efficacy and safety of tranexamic acid in pediatric trauma patients: Evidence from meta-analysis

Mahdi Al-Jeabory, Aleksandra Gasecka, Wojciech Wieczorek, Jaroslaw Mayer-Szary, Milosz J. Jaguszewski, Lukasz Szarpak

PII: S0735-6757(21)00115-7

DOI: https://doi.org/10.1016/j.ajem.2021.02.009

Reference: YAJEM 159819

To appear in: *American Journal of Emergency Medicine*

Received date: 18 January 2021

Revised date: 1 February 2021

Accepted date: 4 February 2021

Please cite this article as: M. Al-Jeabory, A. Gasecka, W. Wieczorek, et al., Efficacy and safety of tranexamic acid in pediatric trauma patients: Evidence from meta-analysis, *American Journal of Emergency Medicine* (2018), https://doi.org/10.1016/j.ajem.2021.02.009

Efficacy and safety of tranexamic acid in pediatric trauma patients: evidence from meta-analysis

Mahdi Al-Jeabory [1], Aleksandra Gasecka [2,3], Wojciech Wieczorek [1,4], Jaroslaw Mayer-Szary[5], Milosz J. Jaguszewski [6], Lukasz Szarpak [1,7,8]

1. Polish Society of Disaster Medicine, Warsaw, Poland
2. 1st Chair and Department of Cardiology, Medical University of Warsaw, Warsaw, Poland
3. Department of Cardiology, University Medical Center Utrecht, Utrecht, The Netherlands
4. Department of Emergency Medicine, Medical University of Warsaw, Warsaw, Poland
5. 1st Department of Cardiology, Medical University of Gdansk, Poland
6. Department of Paediatric Cardiology and Congenital Heart Diseases, Medical University of Gdansk, Gdansk, Poland
7. Maria Sklodowska-Curie Medical Academy in Warsaw, Warsaw, Poland
8. Maria Sklodowska-Cure Bialystok Oncology Centre, Bialystok, Poland

Corresponding author:

Lukasz Szarpak, Assoc Prof. PhD, MBA

Maria Sklodowska-Curie Medical Academy

Solidarnosci 12 Av., 03-411 Warsaw, Poland

e-mail: lukasz.szarpak@gmail.com

Phone: 048500186225

Keywords: tranexamic acid; treatment efficacy; pediatric; trauma; bleeding; mortality

Conflict of interest: None.

To the Editor,

Trauma requiring massive transfusions hinders the successful resuscitation and deteriorates outcomes [1]. Antifibrinolytic therapy has become an emerging standard in the resuscitation of patients in early hemorrhagic shock and should be administered as soon as potentially lethal hemorrhage is suspected [2]. Tranexamic acid (TXA) inhibits plasminogen activation

leading to decreased fibrinolysis [3]. In contrast to previous studies of fresh frozen plasma which needs to be thawed thus delaying the treatment, TXA is easily administered upon admission [3]. TXA has been demonstrated to decrease mortality in adult trauma, particularly in patients requiring massive transfusions [2]. It has also shown significantly reduced blood loss and transfusion requirements in major elective pediatric surgery [4], but limited data are available for the efficacy and safety of TXA in pediatric trauma patients. We performed a systematic review and meta-analysis to verify the efficacy and safety of TXA in pediatric trauma.

The present meta-analysis was performed and reported using the recommendations by Cochrane Collaboration and Preferred Reported Items for Systematic Reviews and Meta-analysis

(PRISMA) guidelines. For inclusion in our analysis, studies had to be trails which compared the TXA vs. non-TXA treatment for pediatric trauma patients. We excluded articles relating to head injuries due to the different pathophysiology of injury as well as different treatment. A comprehensive literature search was performed independently by two reviewers (J.A, M.P.) using PubMed, EMBASE, Scopus and Cochrane Central. There were no restrictions regarding to the language. We include only full research articles. All statistical analyses were performed with Review Manager Software 5.4 (The Cochrane Collaboration, Oxford, Copenhagen, Denmark). All results are presented as mean difference (MD) or odds ratio (OR) with 95% confidence interval (CI). When the continuous outcome was reported in a study as median, range, and interquartile range, we estimated means and standard deviations using the formula described by Hozo et al. [5]. The random-effects model was used for $I^2 > 50\%$. Statistical testing was two-tailed. $P < 0.05$ was considered statistically significant. Finally, four studies meet the inclusion criteria and were included in meta-analysis (Supplementary File) [6-9]. All studies were published between 2014 and 2020. There was a total of 8,751 pediatric patients.

In-hospital mortality was reported in all four studies. In-hospital mortality in the TXA group was 1.8% compared with 3.6% for non-TXA group (OR=1.77; 95%CI: 0.32, 9.73; P = 0.51; $I^2 = 92\%$; Figure 1). Moreover, studies showed that seizures occurred in 0.4% in TXA group compared to 0% for non-TXA group (OR = 15.06; 95%CI: 0.86, 263.78; P=0.06). The use of TXA versus the non-TXA group was associated with a comparative risk of thromboembolism (0.3% vs. 0.2%; OR=0.0.72; 95%CI: 0.19, 2.70; P=0.62) and renal dysfunction (0.2% vs. 0%; OR=7.01; 95%CI: 0.36, 135.82; P=0.20).

In conclusion, we demonstrated that the administration of TXA for pediatric trauma patients does not significantly affect in-hospital outcomes and is associated with a higher risk of seizures and a trend towards lower risk of thromboembolism. Our meta-analysis did not confirm the favorable effects of TXA on mortality, observed in adult trauma patients. However, you should be aware that in the case of head injuries, both the survival rate and potential complications of using TXA may be different [10]. There is an urgent need for further pediatric research on the appropriate patient selection who might potentially benefit from TXA administration.

References:

1. Safiejko K, Smereka J, Filipiak KJ, et al. Effectiveness and safety of hypotension fluid resuscitation in traumatic hemorrhagic shock: a systematic review and meta-analysis of randomized controlled trials. Cardiol J. 2020 Jul 10. doi: 10.5603/CJ.a2020.0096.
2. Morrison JJ, Dubose JJ, Rasmussen TE, Midwinter MJ. Military application of tranexamic acid in trauma emergency resuscitation (MATTERs) study. Arch Surg. 2012; 147(2):113-9. doi: 10.1001/archsurg.2011.287.

3. Porta CR, Nelson D, McVay D, et al. The effects of tranexamic acid and prothrombin complex concentrate on the coagulopathy of trauma: an in vitro analysis of the impact of severe acidosis. J Trauma Acute Care Surg. 2013; 75(6):954-60. doi: 10.1097/TA.0b013e31829e20bf.
4. Goobie SM, Faraoni D. Tranexamic acid and perioperative bleeding in children: what do we still need to know? Curr Opin Anaesthesiol. 2019; 32(3):343-352. doi: 10.1097/ACO.0000000000000728.
5. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. BMC Med Res Methodol. 2005; 5:13. doi: 10.1186/1471-2288-5-13.
6. Eckert MJ, Wertin TM, Tyner SD, Nelson DN, Izenberg S, Martin MJ. Tranexamic acid administration to pediatric trauma patients in a combat setting: the pediatric trauma and tranexamic acid study (PED-TRAX). J Trauma Acute Care Surg. 2014; 77(6):852-8; discussion 858. doi: 10.1097/TA.0000000000000443.
7. Hamele M, Aden JK, Borgman MA. Tranexamic acid in pediatric combat trauma requiring massive transfusions and mortality. J Trauma Acute Care Surg. 2020 Aug;89(2S Suppl 2):S242-S245. doi: 10.1097/TA.0000000000002701.
8. Maeda T, Michihata N, Sasabuchi Y, et al. Safety of Tranexamic Acid During Pediatric Trauma: A Nationwide Database Study. Pediatr Crit Care Med. 2018; 19(12):e637-e642. doi: 10.1097/PCC.0000000000001724.
9. Thomson JM, Huynh HH, Drone HM, et al. Experience in an Urban Level 1 Trauma Center With Tranexamic Acid in Pediatric Trauma: A Retrospective Chart Review. J Intensive Care Med. 2020; 885066619890834. doi: 10.1177/0885066619890834.
10. Rowell SE, Meier EN, McKnight B, et al. Effect of Out-of-Hospital Tranexamic Acid vs Placebo on 6-Month Functional Neurologic Outcomes in Patients With Moderate or Severe Traumatic Brain Injury. JAMA. 2020; 324(10):961-974. doi: 10.1001/jama.2020.8958.

Figure legend

Figure 1. Forest plot of patients in-hospital mortality in TXA and not-TXA group. The center of each square represents the weignted mean difference for individual trials, and the corresponding horizontal line stands for a 95% confidence interval. The diamonds represent pooled results.

Study or Subgroup	TXA Events	TXA Total	Non-TXA Events	Non-TXA Total	Weight	Odds Ratio M-H, Random, 95% CI
Eckert 2014	10	66	5	700	24.6%	24.82 [8.20, 75.13]
Hamele 2020	5	59	83	448	25.3%	0.41 [0.16, 1.05]
Maeda 2018	13	1914	18	1914	26.2%	0.72 [0.35, 1.47]
Thomson 2019	10	29	5	19	23.8%	1.47 [0.41, 5.28]
Total (95% CI)		**2068**		**3081**	**100.0%**	**1.77 [0.32, 9.73]**
Total events	38		111			

Heterogeneity: $Tau^2 = 2.75$; $Chi^2 = 36.22$, df = 3 ($P < 0.00001$); $I^2 = 92\%$

Test for overall effect: $Z = 0.65$ ($P = 0.51$)

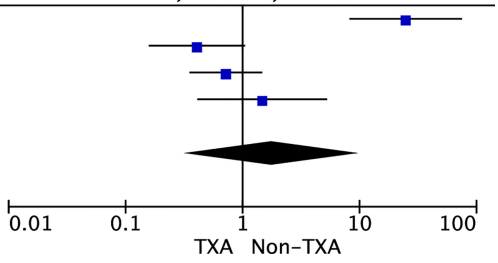

Figure 1