EMPoweRx
conference

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Emergency Medicine Pharmacotherapy with Resuscitation (EMPoweRx) Conference

Tranexamic Acid in the Trauma Patient

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March 12, 2022

Disclosure

- I have nothing to disclose

Objectives

- Review the etiology and pathophysiology of trauma induced coagulopathy
- Recall the pharmacology of tranexamic acid (TXA)
- Analyze the literature regarding the use of TXA in trauma patients

Acute Coagulopathy of Trauma

- Hemorrhage is the most preventable cause of death and accounts for ~40% of all trauma deaths
- Complex multifactorial process
- Mediated by tissue hypoperfusion and direct activation of protein c pathway
- 1/3 of injured patients are coagulopathic
- 4-fold increase in mortality

Hess J, et. al. *J Trauma.* 2008;65:748–754. Cohen M, et. al. *Crit Care Clin.* 2017; 133: 101 – 118. *Kafarani H, et. al. Scandinavian Journal of Surgery.* 2014; 103: 81 – 88. Dyer M, Neal M. Ch. 5: Defining the Lethal Triad. 2017: pp 41 – 53. Cannon J. *NEJM.* 2018; 378: 370 – 379. Hanley C. Br J Anaesth. 2021; 126(1): 12-17.

Question

Hemorrhage is the most common cause of preventable death after trauma

- True
- False

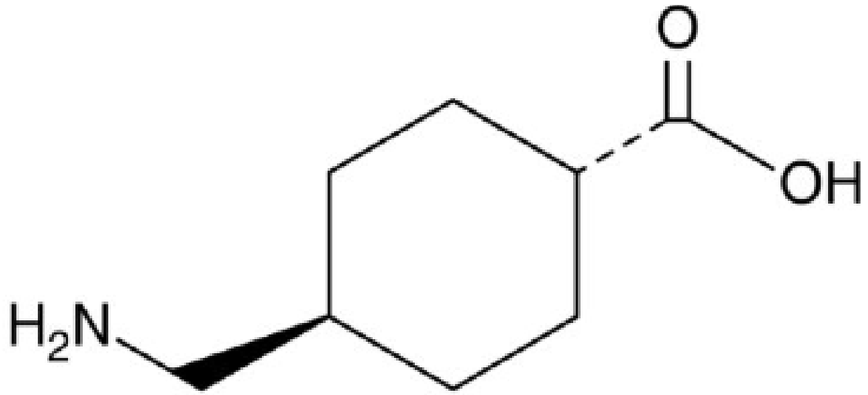
Pharmacology of TXA

1986
- FDA approved for prevention or reduction of bleeding in patients with hemophilia undergoing dental procedures

Class
- Antifibrinolytic

MOA
- Inhibition of both plasminogen activation and plasmin activity

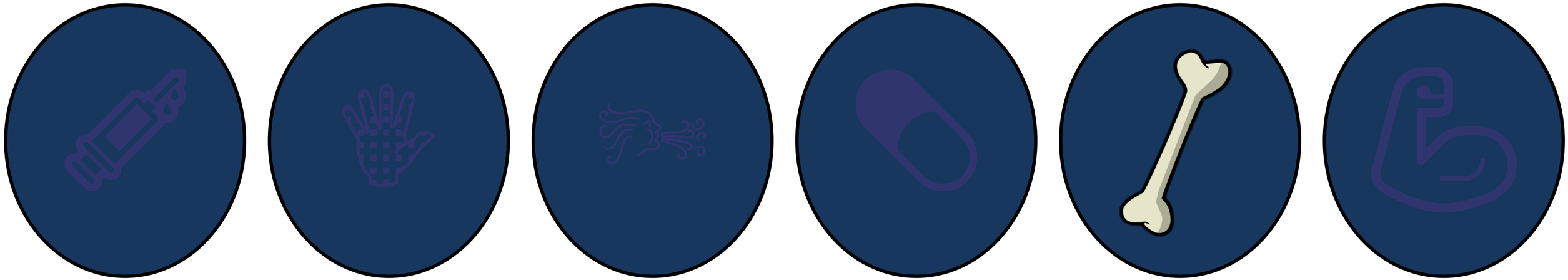
Trans-4-(aminomethyl)cyclohexanecarboxylic acid



TXA End Game:
Prevent clot breakdown and stabilize existing clots

Tranexamic acid [package insert]. New York, NY: Pfizer, INC; 2021.
Cap AP. *J Trauma.* 2011; 71: S9 – S14. Dunn C. *Drugs.* 1999: 57(6): 1005 – 1032.
Reed R. *Continuing Education in Anaesthesia Critical Care and Pain.* 2015; 15(1): 32 – 37.
Wu T. *PLoS ONE.* 2020; 15(5): 1 – 11.

Pharmacotherapy Considerations of TXA



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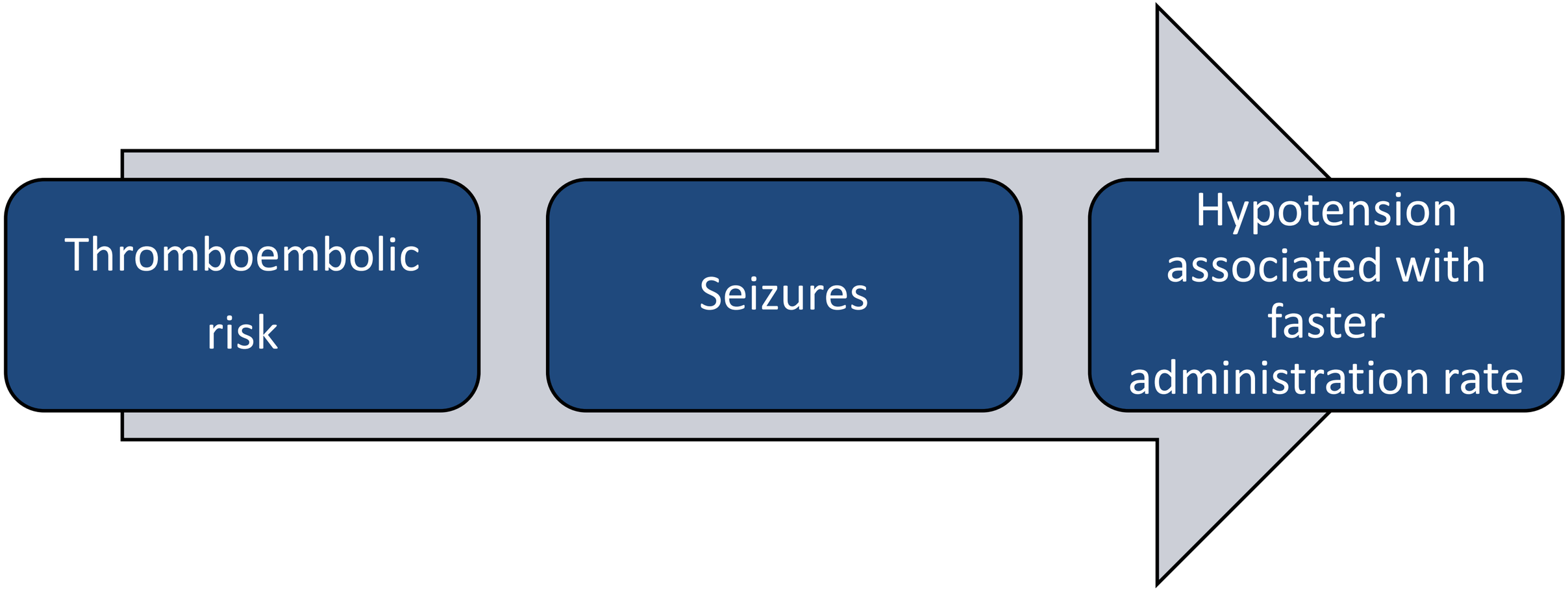
Grassin-Delyle S. *Br J Anaesth.* 2021; 126(1): 201-209.
Androski C. *J Spec Oper Med.* 2020;20(4): 85–91.
TCCC Guidelines for Medical Personnel. 2021.

Potential Side Effects



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Lysteda™ (tranexamic acid) [package insert]. Parisppany, NJ: Ferring Pharmaceuticals INC; 2013.
Murao S. Crit Care. 2021; 25(1): 380.
Murdaca G. Clin Mol Allergy. 2020; 3;18:16.

- Who?
- What?
- When?
- Where?
- Why?
- How?

Question

TXA promotes clot formation

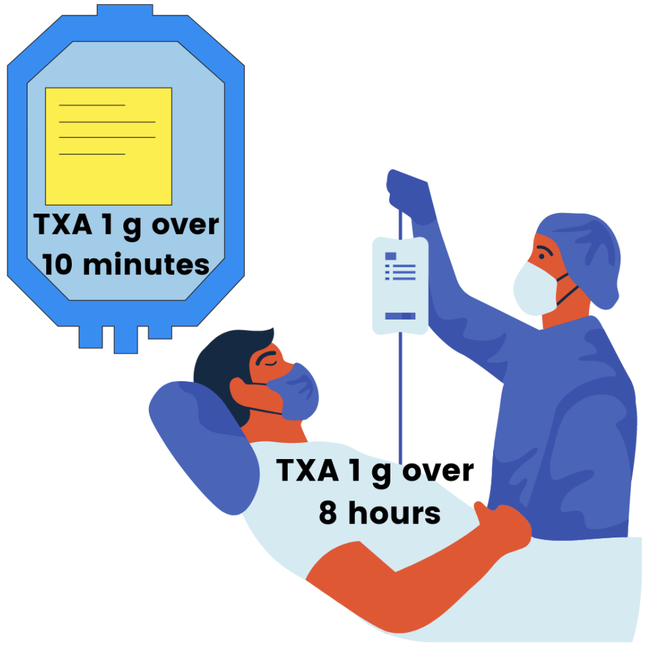
- True
- False

TXA does not promote clot formation, rather it prevents clot breakdown

CRASH-2

Clinical Randomization of an Antifibrinolytic in Significant Hemorrhage

20,211 patients



Death within 4 weeks of injury

Shakur H. *Lancet.* 2010; 376: 23–32.

CRASH-2 Trial Results

Outcomes	TXA (n = 10,060)	Placebo (n = 10,067)	RR (95% CI)	P value
All cause mortality	1,463 (14.5%)	1,613 (16%)	0.91 (0.85 - 0.97)	0.0035
occlusive event	168 (1.7%)	201 (2%)	(0.68 – 1.02)	0.084
Blood product transfused	5,067 (50.4%)	5,160 (51.3%)	0.98 (0.96 – 1.01)	0.21

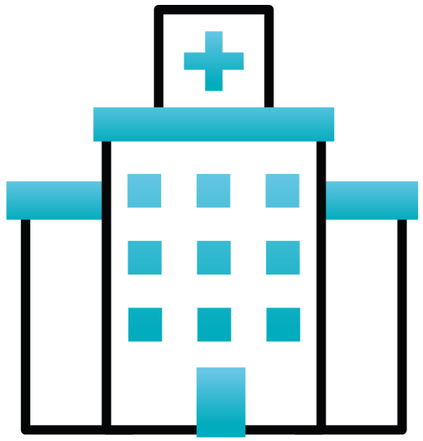
An exploratory analysis comparing time to treatment and death due to bleeding found that patients treated with TXA within 3 hours had a decreased risk of death due to bleeding while patients treated with TXA greater than 3 hours had an increased risk of death due to bleeding.

Shakur H. *Lancet.* 2010; 376: 23–32.
Roberts I. *Lancet.* 2011; 377: 1096–101.

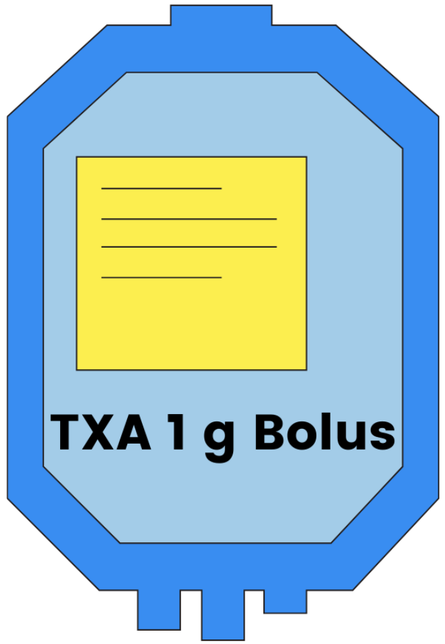
MATTERs Trial

Military Application of Tranexamic Acid in Trauma Emergency Resuscitation

Camp Bastion



896 patients



Death at 24 hours, 48 hours, and 30 days

Morrison J. *Arch Surg*. 2012; 147(2): 113-119.

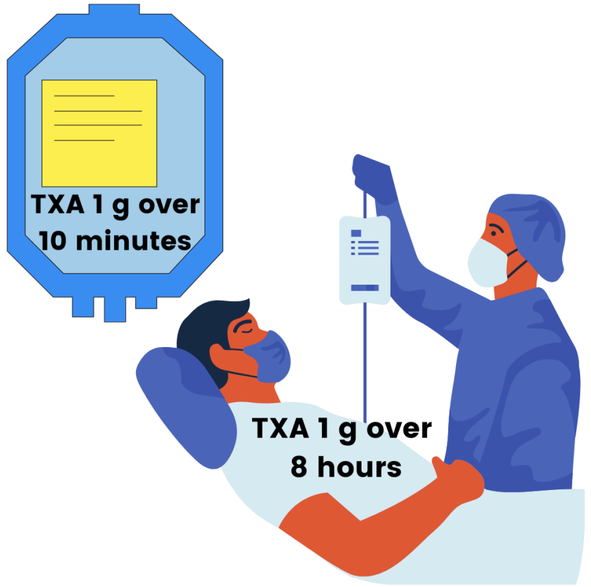
MATTERs Trial Results

Overall Cohort of Patients (Mortality, %)			
Outcomes	TXA (n = 296)	No TXA (n = 603)	p value
Mortality < 24 hours	293 (9.6%)	603 (12.4%)	0.2
Mortality < 48 hours	264 (11.3%)	507 (18.9%)	0.004
In hospital mortality	264 (17.4%)	603 (23.9%)	0.03
TXA and Massive Transfusion (Mortality, %)			
	TXA (n = 125)	No TXA (n = 196)	
Mortality < 24 hours	125 (9.6%)	196 (14.8%)	0.17
Mortality < 48 hours	112 (10.4%)	160 (23.5%)	0.003
In hospital mortality	125 (14.4%)	196 (28.1%)	0.004

Overall Cohort of Patients			
Adverse Events	TXA (n = 296)	No TXA (n = 603)	p value
DVT	7 (2.4%)	1 (0.2%)	0.001
PE	8 (2.7%)	2 (0.3%)	0.001
TXA and Massive Transfusion			
	TXA (n = 125)	No TXA (n = 196)	p value
DVT	2 (1.6%)	1 (0.5%)	0.32
PE	4 (3.2%)	0	0.01

Morrison J. *Arch Surg*. 2012; 147(2): 113-119.

Do all Trauma Patients Benefit from TXA?



Does early routine use of TXA in critically injured trauma patients improve outcomes?

Valle E. *J Trauma Acute Care Surg*. 2014;76: 1373 - 1378.

Results

97 min

- Median time to TXA administered after arrival (range 0 – 886 minutes)

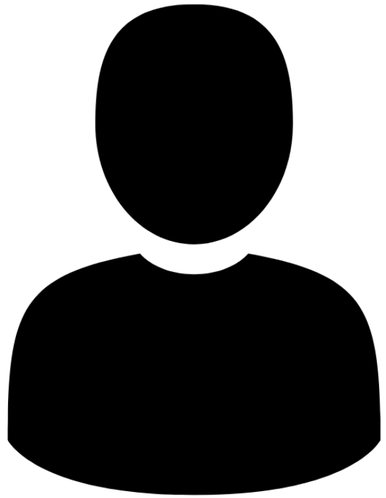
Mortality

- 27% in the TXA group versus 17% in the no TXA group (p = 0.024)

Conclusions

- No effect on mortality across all subgroups

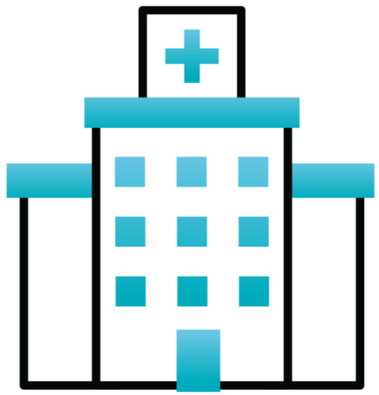
150 patients



Valle E. *J Trauma Acute Care Surg*. 2014;76: 1373 - 1378.

TXA Use in Severely Injured Civilian Patients and the Effects on Outcomes

Urban Trauma Center



385 patients

Effect of TXA on mortality

Cole E. *Ann Surg.* 2015; 261: 390–394.

Results

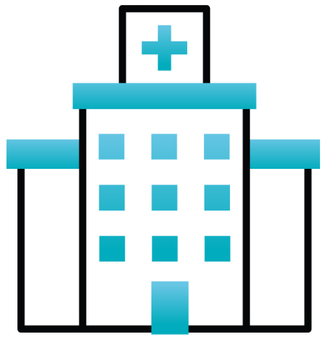
Outcomes	No TXA (n = 225)	TXA (n = 160)	No Shock No TXA (n = 178)	No Shock TXA (n = 76)	Shock No TXA (n = 47)	Shock TXA (n = 84)
Mortality ≤ 48 hours (%)	18 (8)	13 (8)	10 (6)	4 (5)	8 (15)	9 (11)
Mortality > 48 hours (%)	18 (8)	17 (11)	15 (9)	7 (9)	4 (8)	9 (11)
VTE (%)	9 (4)	8 (5)	7 (4)	1 (1)	2 (2)	7 (8)*
Stroke (%)	3 (1)	5 (3)	1 (1)	1 (1)	2 (4)	4 (5)
MI (%)	3 (1)	3 (2)	1 (1)	0	2 (4)	3 (4)

*$p < 0.05$

Cole E. *Ann Surg.* 2015; 261: 390–394.

Does Liberal Pre-hospital and In-hospital TXA Influence Outcome in Severely Injured Patients?

University Medical Center, Utrecht



422 patients

Effect of TXA on morbidity and mortality

van Wessem K. *World J Surg*. 2021; 45: 2398–2407.

Results

Outcomes	TXA (n = 280)	No TXA (n = 142)	p value
Mortality	56 (20)	23 (16)	0.36
Thrombo-embolic complications	25 (9)	7 (5)	0.18

van Wessem K. *World J Surg*. 2021; 45: 2398–2407.

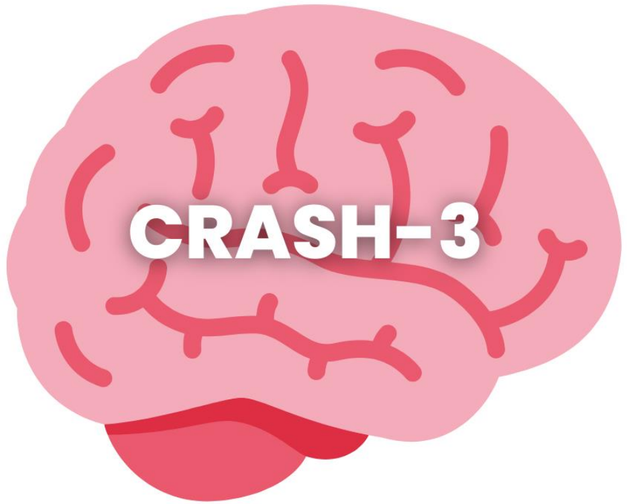
Question

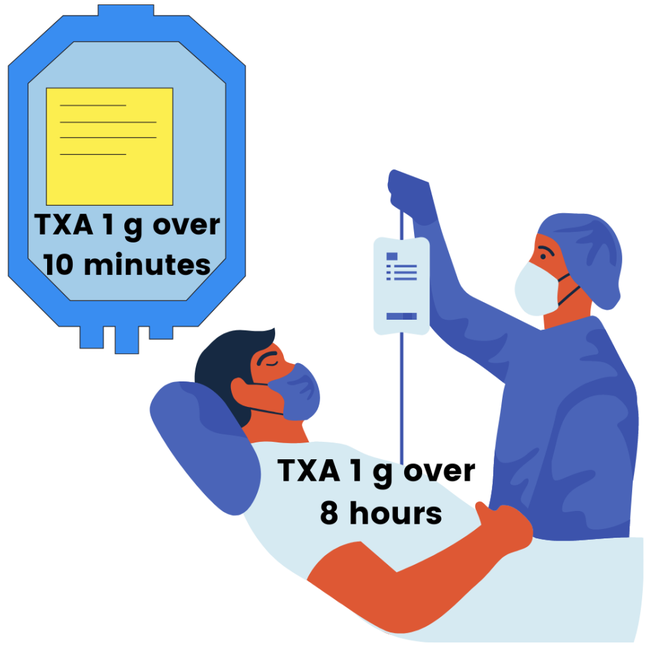
It is recommended to use TXA at any time after a trauma has occurred

- True
- False

TXA should be used within 3 hours of injury

TXA in Traumatic Brain Injury





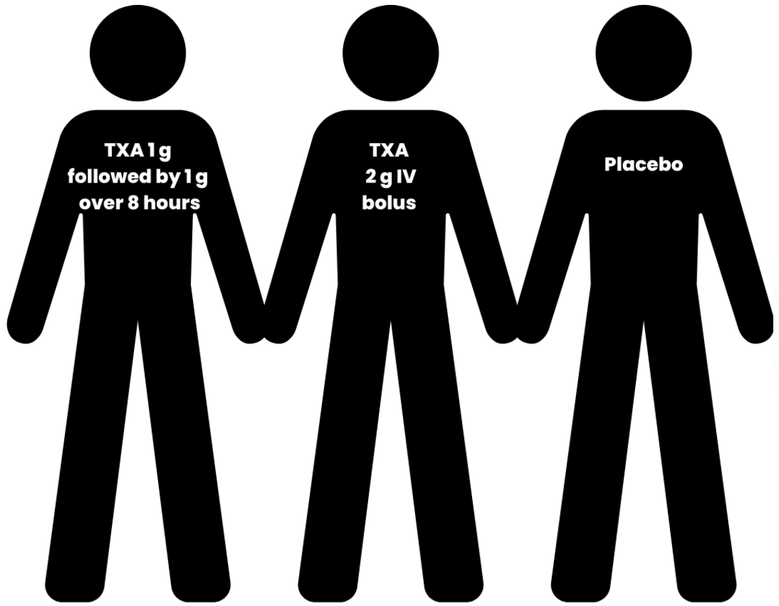
Death within 28 days of injury

Results: Reduction in death in the mild-to-moderate head injury group when compared to placebo; however, not seen in patients with severe head injury

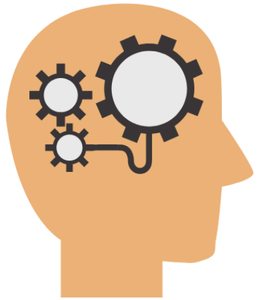
Roberts I. *Lancet.* 2019; 394: 1713–23.

Effect of Out-of-Hospital TXA in TBI

12 regions in the US and Canada



Functional Neurological Outcome at 6 months



Results: No significant difference in 6-month neurological outcome

Rowell S. *JAMA.* 2020; 324(10): 961-974.

Addition of TXA to a Traumatic Injury Massive Transfusion Protocol

- Boston Medical Center
- Training and education, guideline development, and order sets
- 16 month analysis
- Multidisciplinary collaboration and standardization increased use of TXA in trauma patients requiring MTP

Farrell N. *Am J Health-Syst Pharm*. 2015; 72: 1059-64.

Logistical Considerations

- Involve all interested parties
- Create algorithms/ordersets
- Location
- Education

Conclusions

- TXA is an antifibrinolytic agent that may be used in trauma for patients who present with hemorrhagic shock
- TXA should be administered within 3 hours of injury
- TXA administered more than 3 hours from injury should be avoided
- Role of TXA in advanced trauma centers remains to be elucidated

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Questions?

Thank You

References

- Hess J, Brohi K, Dutton R, Hauser C, Holcomb J, et. al. The coagulopathy of trauma: a review of mechanisms. *J Trauma.* 2008. 65: 748–754.
- Kaffarani H, Velmahos G. Damage control resuscitation in trauma. *Scandinavian Journal of Surgery.* 2014; 103: 81 – 88.
- Cohen M, Christie S. Coagulopathy of trauma. *Crit Care Clin.* 2017; 133: 101 – 118.
- Dyer M, Neal M. Ch. 5: Defining the Lethal Triad. Damage Control Management in the Polytrauma Patient. 2nd ed. 2017: pp 41 – 53.
- Cannon J. Hemorrhagic shock. *NEJM*. 2018; 378: 370 – 379.
- Tranexamic acid [package insert]. New York, NY: Pfizer, INC; 2021.
- Lysteda™ (tranexamic acid) [package insert]. Parisppany, NJ: Ferring Pharmaceuticals INC; 2013.
- Cap AP, et. al. Tranexamic acid for trauma patients: a critical review of the literature. *J Trauma.* 2011; 71: S9 – S14.
- Dunn C, Goa K. Tranexamic acid: a review of its use in surgery and other indications. *Drugs.* 1999: 57(6): 1005 – 1032.
- Reed R, Woolley T. Uses of tranexamic acid. *Continuing Education in Anaesthesia Critical Care and Pain*. 2015; 15(1): 32 – 37.
- Wu T, et. al. Computational model of tranexamic acid on urokinase mediated fibrinolysis. *PLoS ONE*. 2020; 15(5): 1 – 11.

References

- Grassin-Delyle S, Shakur-Still H, Picetti R, et. al. Pharmacokinetics of intramuscular tranexamic acid in bleeding trauma patients: a clinical trial. *Br J Anaesth*. 2021; 126(1): 201-209.
- Androski C, Bianchi W, Robinson DL, Zarow GJ, Moore CH, Deaton T, et al. Case Series on 2g Tranexamic Acid Flush From the 75th Ranger Regiment Casualty Database. *J Spec Oper Med.* 2020;20(4): 85–91.
- Joint Trauma System. Clinical Practice Guidelines. Tactical Combat Casualty Care (TCCC) Guidelines for Medical Personnel. December 2021.
- Murao S, Nakata H, Roberts I, Yamakawa K. Effect of tranexamic acid on thrombotic events and seizures in bleeding patients: a systematic review and meta-analysis. *Crit Care*. 2021; 25(1): 380.
- Murdaca G, Greco M, Vassallo C, Gangemi S. Tranexamic acid adverse reactions: a brief summary for internists and emergency doctors. *Clin Mol Allergy.* 2020; 3;18:16.

References

- Hanley C, Callum J, Jerath A. Tranexamic acid and trauma coagulopathy: where are we now? *Br J Anaesth.* 2021; 126(1): 12-17.
- Shakur H, Roberts I, Bautista R, et. al. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. *Lancet.* 2010; 376: 23–32.
- Roberts I, Shakur H, Afolabi A, et. al. The importance of early treatment with tranexamic acid in bleeding trauma patients: an exploratory analysis of the CRASH-2 randomised controlled trial. *Lancet.* 2011; 377: 1096–101.
- Morrison J, Dubose J, Rasmussen T, Midwinter M. Military Application of Tranexamic Acid in Trauma Emergency Resuscitation (MATTERs) Study. *Arch Surg*. 2012; 147(2): 113-119.
- Valle E, Allen C, Van Haren R, et. al. Do all trauma patients benefit from tranexamic acid? *J Trauma Acute Care Surg*. 2014;76: 1373 - 1378.
- Cole E, Davenport R, Willett K, Brohi K. Tranexamic acid use in severely injured civilian patients and the effects on outcomes: a prospective cohort study. *Ann Surg.* 2015; 261: 390–394.
- van Wessem K, Leenen L. Does Liberal Prehospital and In-Hospital Tranexamic Acid Influence Outcome in Severely Injured Patients? A Prospective Cohort Study. *World J Surg*. 2021; 45: 2398–2407.
- Roberts I, Shakur-Still H, Aeron-Thomas A, et. al. Effects of tranexamic acid on death, disability, vascular occlusive events and other morbidities in patients with acute traumatic brain injury (CRASH-3): a randomised, placebo-controlled trial. *Lancet.* 2019; 394: 1713–23.
- Rowell S, Meier E, 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.
- Farrell N, Wing H, Burke P, Huiras P. Addition of tranexamic acid to a traumatic injury massive transfusion protocol. *Am J Health-Syst Pharm*. 2015; 72: 1059-64.