Optimizing the Tranexamic Acid Dose for Prophylactic Use to Improve Hemostasis Post-injury

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Research was conducted in compliance with Animal Welfare Act, the implementing Animal Welfare regulations, and the principles of the Guide for the Care and Use of Laboratory Animals. The Institutional Animal Care and Use Committee approved all research conducted in this study. The facility where this research was conducted is fully accredited by the AAALAC International.

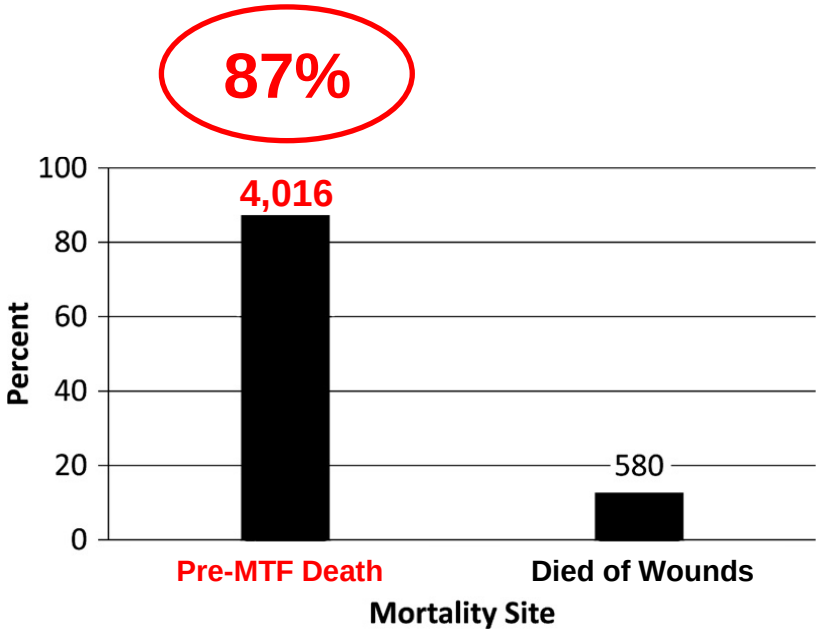
Agenda

Purpose: Tranexamic acid dose optimization

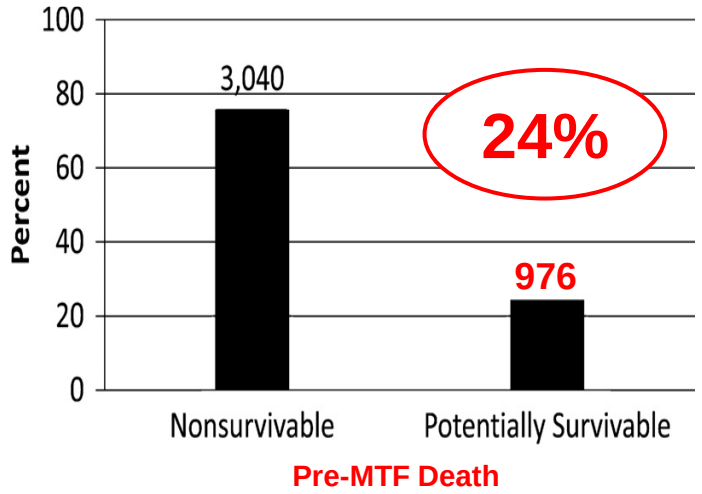
- Background
- Objective
- Study Design
- Results

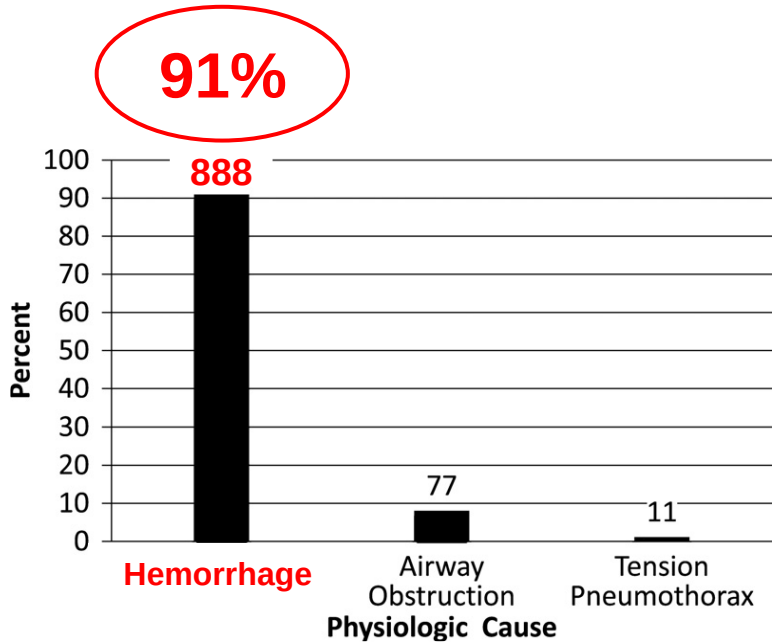
Background

Military Casualty



Eastridge BJ, et al. J Trauma Acute Care Surg. 2012.

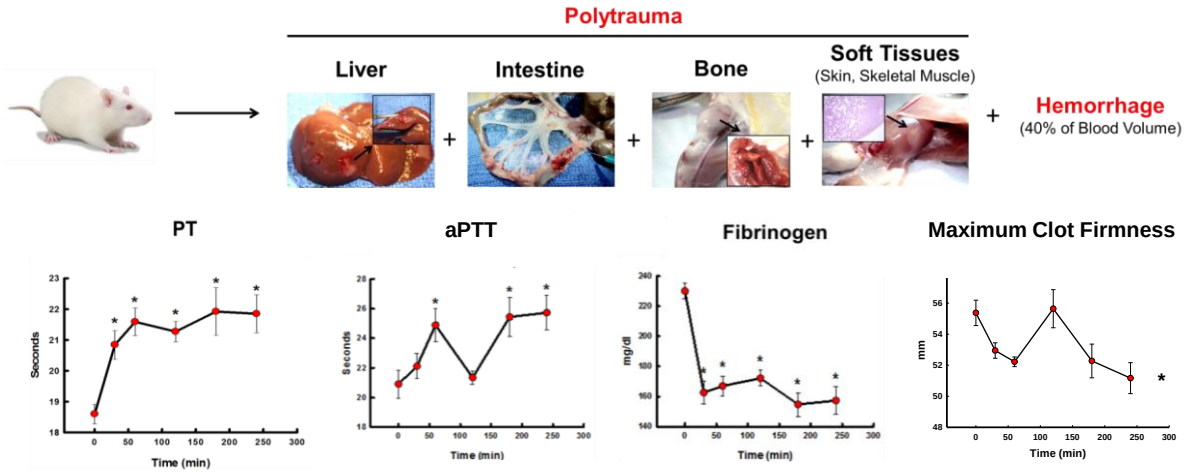




Hemorrhage remains the leading cause of preventable death in military casualties. New approaches are needed that can extend pre-hospital survival time and reduce mortality due to shock.

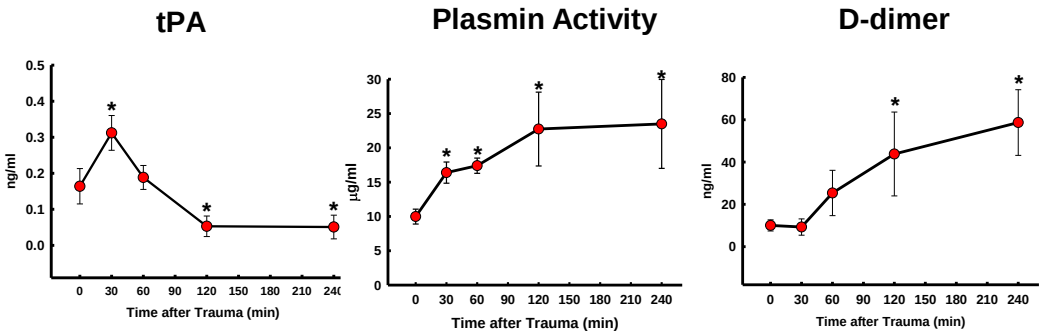
Background

Acute Traumatic Coagulopathy



Darlington DN, Shock 2013

Hyperfibrinolysis



Wu X, Am J Physiol Regul Integr Comp Physiol 2016

J Trauma Acute Care Surg. Author manuscript; available in PMC: 2019 Jun 1.

Published in final edited form as: J Trauma Acute Care Surg. 2018 Jun;84(6):929–938. doi: 10.1097/TA.0000000000001878

Systemic Hyperfibrinolysis after Trauma: A Pilot study of Targeted Proteomic Analysis of Superposed Mechanisms in Patient Plasma

Anirban Banerjee [1,*], Christopher C Silliman [1,2,5,*], Ernest E Moore [1,6], Monika Dzieciatskowa [6], Marguerite Kelher [1,5], Angela Sauaia [1,6], Kenneth Jones [2], Michael P Chapman [4], Eduardo Gonzalez [1,6], Hunter B Moore [1,6], Angelo D'Alessandro [6], Erik Peltz [1], Benjamin E Huebner [1,6], Peter Einerson [1,6], James Chandler [1,6], Arsen Ghasabayan [1,6], Kirk Hansen [3]

Hyperfibrinolysis, physiologic fibrinolysis, and fibrinolysis shutdown

The spectrum of postinjury fibrinolysis and relevance to antifibrinolytic therapy

Moore, Hunter B. MD; Moore, Ernest E. MD; Gonzalez, Eduardo MD; Chapman, Michael P. MD; Chin, Theresa L. MD; Silliman, Christopher C. MD, PhD; Banerjee, Anirban PhD; Sauaia, Angela MD, PhD

Author Information

Journal of Trauma and Acute Care Surgery 77(6):p 811-817, December 2014. | *DOI:* 10.1097/TA.0000000000000341

EAST 2017 PLENARY PAPER

The hyperfibrinolytic phenotype is the most lethal and resource intense presentation of fibrinolysis in massive transfusion patients

Taylor, John R. III MD; Fox, Erin E. PhD; Holcomb, John B. MD; Rizoli, Sandro MD, PhD; Inaba, Kenji MD; Schreiber, Martin A. MD; Brasel, Karen MD, MPH; Scalea, Thomas M. MD; Wade, Charles E. PhD; Bulger, Eileen MD; Cotton, Bryan A. MD, MPH

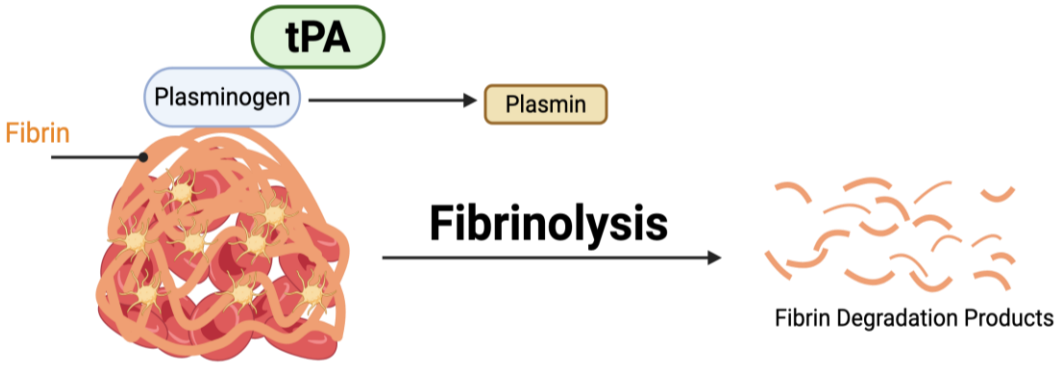
Author Information

Journal of Trauma and Acute Care Surgery 84(1):p 25-30, January 2018. | *DOI:* 10.1097/TA.0000000000001699

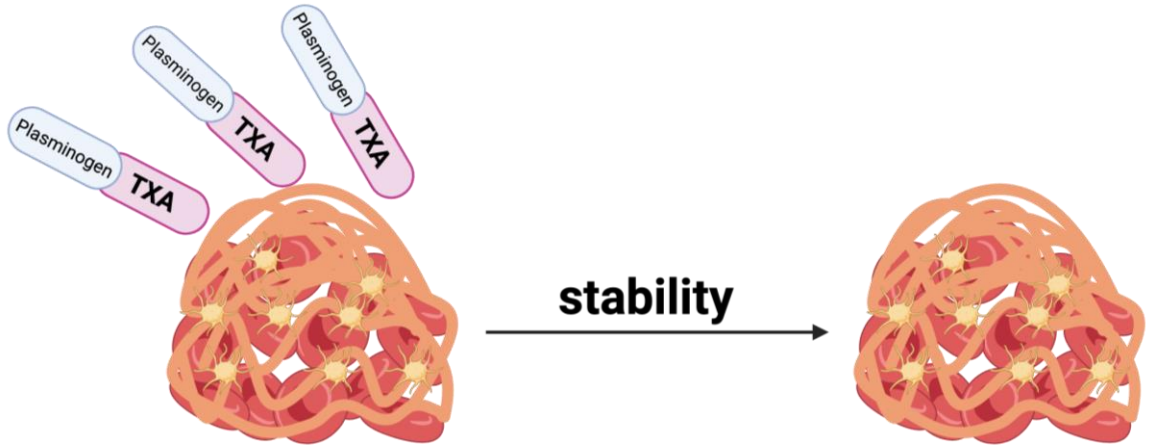
Background

Tranexamic Acid (TXA)

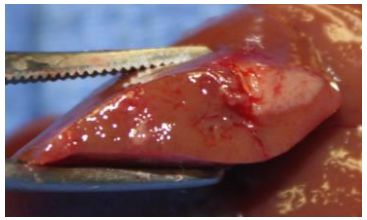
tPA Induced-Fibrinolysis



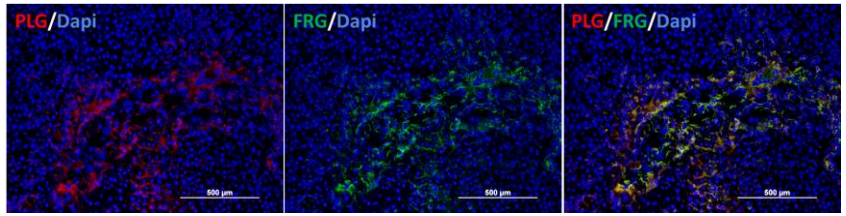
TXA's Antifibrinolytic Activity



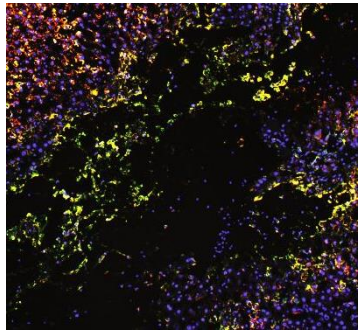
Traumatized Liver



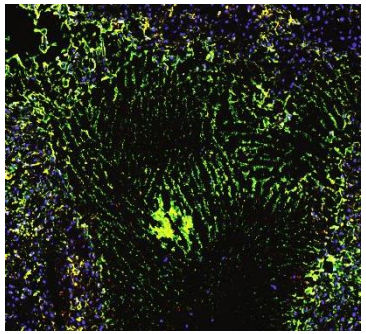
Deposition of Plasminogen and Fibrin Immediately after Trauma



2hr after Trauma



2hr after Trauma with TXA Pretreatment



Wu X, Plos One 2017

Background

Randomized Controlled Trial > Lancet. 2011 Mar 26;377(9771):1096-101, 1101.e1-2.
doi: 10.1016/S0140-6736(11)60278-X.

The importance of early treatment with tranexamic acid in bleeding trauma patients: an exploratory analysis of the CRASH-2 randomised controlled trial

CRASH-2 collaborators [1]; Ian Roberts, Haleema Shakur, Adefemi Afolabi, Karim Brohi, Tim Coats, Yashbir Dewan, Satoshi Gando, Gordon Guyatt, B J Hunt, Carlos Morales, Pablo Perel, David Prieto-Merino, Tom Woolley

PMID: 21439633 DOI: 10.1016/S0140-6736(11)60278-X

	N	All causes of death	Bleeding death	Non-bleeding death
Overall	20127	0·91 (0·85–0·97); p=0·0035	0·85 (0·76–0·96); p=0·0077	0·94 (0·86–1·02); p=0·13
Time to treatment (h)				
≤1	7451	0·87 (0·76–0·97)	0·68 (0·57–0·82)	1·04 (0·89–1·21)
>1–3	6033	0·87 (0·77–0·97)	0·79 (0·64–0·97)	0·91 (0·78–1·05)
>3	6634	1·00 (0·90–1·13)	1·44 (1·12–1·84)	0·89 (0·78–1·02)
χ^2 test of homogeneity	..	4·411 (p=0·11)	23·516 (p=0·0000)	2·537 (p=0·28)

Table 1: Relative risk (95% CI) of death with tranexamic acid, overall and by time to treatment

META-ANALYSES

A Single Preoperative Dose of Tranexamic Acid Reduces Perioperative Blood Loss

A Meta-analysis

Heyns, Mieke MD; Knight, Paige MD; Steve, Anna K. MD; Yeung, Justin K. MD

Annals of Surgery 273(1):p 75-81, January 2021. | *DOI:* 10.1097/SLA.0000000000003793

TABLE 1 - Blood Loss in Tranexamic Acid Versus Placebo Groups Based on Surgical Discipline

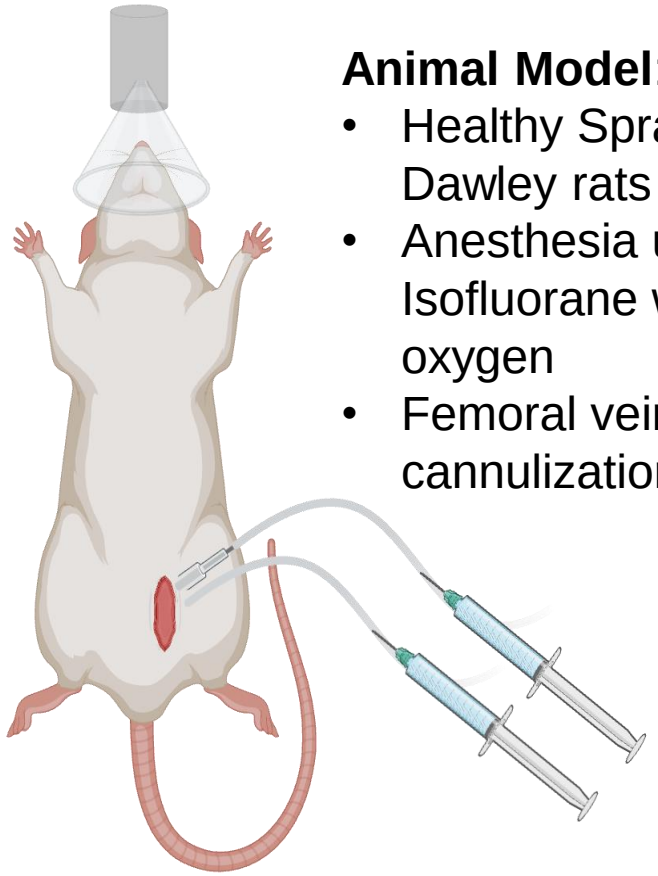
Discipline	No. of RCTs	No. of Patients	Mean Difference in Blood Loss, cc (TXA, Control, 95% CI)
Orthopedic	27	1822	−86.79 [−113.75, −59.83]
Obstetrics and gynecology	16	2850	−166.92 [−198.82, −135.03]
Plastic surgery	1	50	−409.00 [−600.97, −217.03]
Oral maxillofacial/ Otolaryngology	10	776	−222.72 [−290.52, −154.91]
Cardiac surgery	3	200	−331.00 [−379.09, −282.91]
Total	57	5698	−153.33 [−187.79, −118.87]

Prophylactic use of TXA has not been established in combat casualty care, and optimal prophylactic dosing remains unknown.

Objective

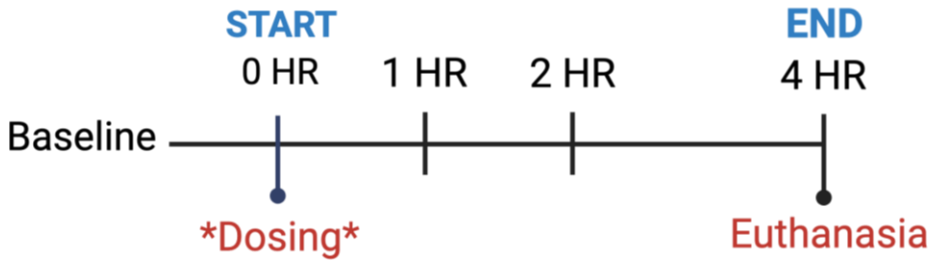
- Investigate a dosing range of prophylactic administration of TXA in healthy rats to determine the best regimens with sustained antifibrinolytic effect.

Study Design



Animal Model:

- Healthy Sprague-Dawley rats
- Anesthesia using Isofluorane with 100% oxygen
- Femoral vein and artery cannulization



Treatment: n = 5/group

- vehicle, 20, 50, 100, 200, or 300 mg/kg (via IV)

Sampling:

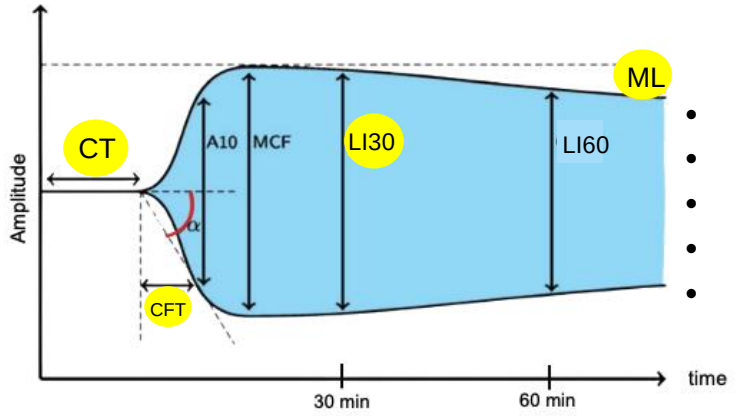
- baseline, 1, 2, and 4 hours after dosing

Analyses:

- Hemodynamics, Blood gas analysis
- LC/MS
- tPA Challenge Test (ROTEM-EXTEM)

Rotational Thromboelastometry (ROTEM) Overview

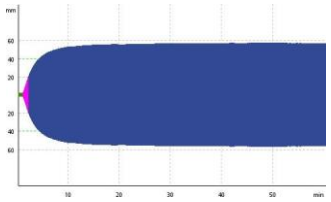
ROTEM is a whole blood assay used to assess hemostatic function by evaluating clot formation, stability, and breakdown.



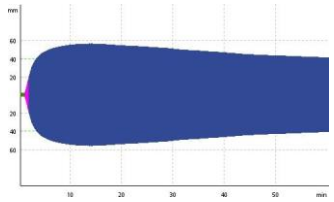
- Clotting Time (CT)
- Clot Forming Time (CFT)
- Maximum Clot Firmness (MCF)
- Clot Lysis Index at 30 minutes (LI30)
- Maximum Lysis (ML)

<u>tPA challenge dosing:</u>

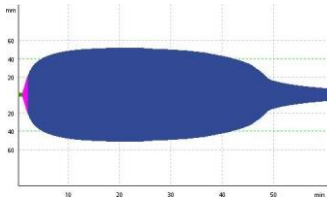
0 µg/ml



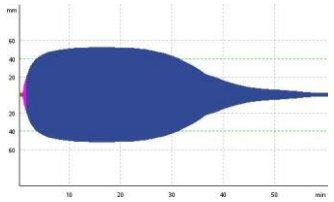
0.5 µg/ml



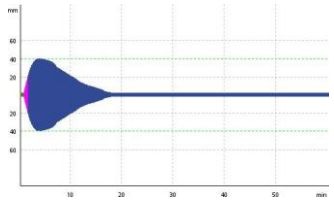
1 µg/ml



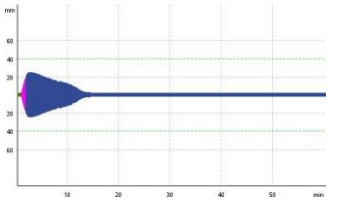
2 µg/ml



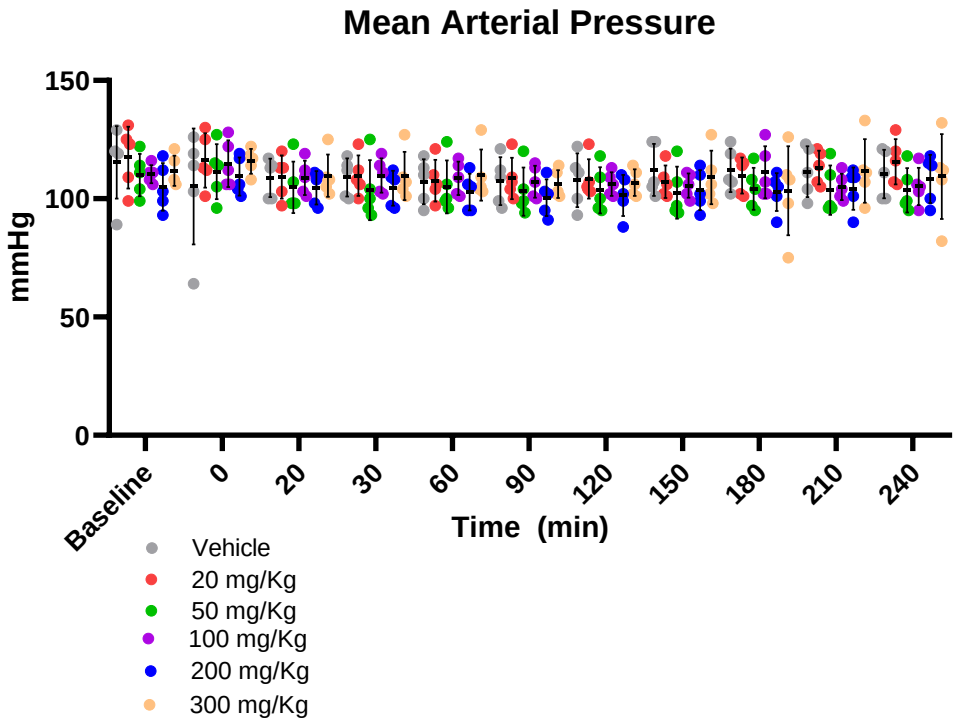
4 µg/ml

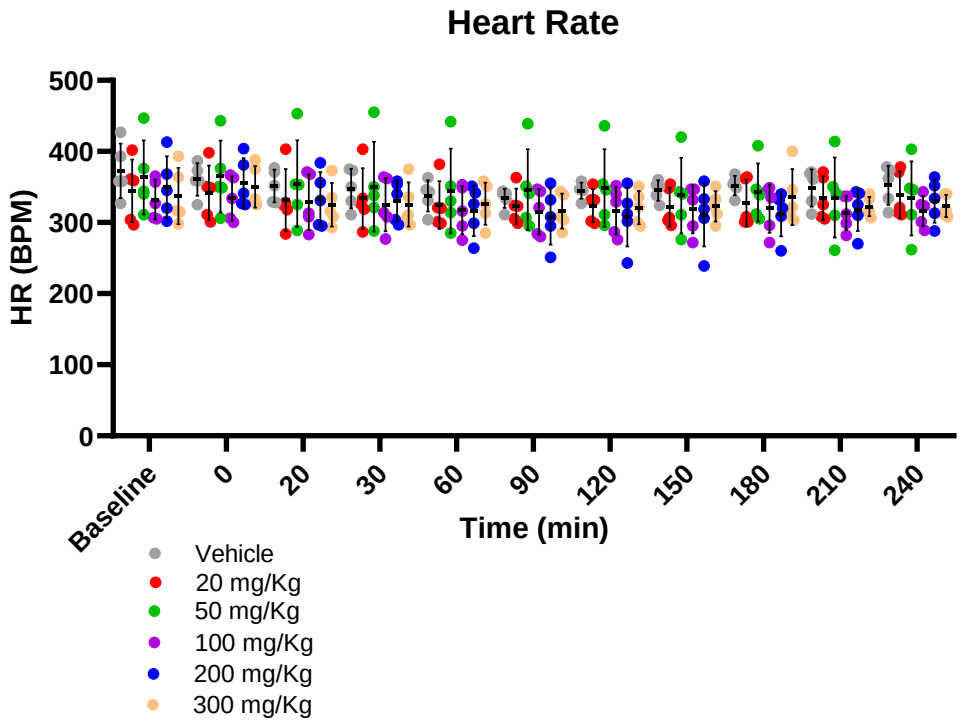


8 µg/ml



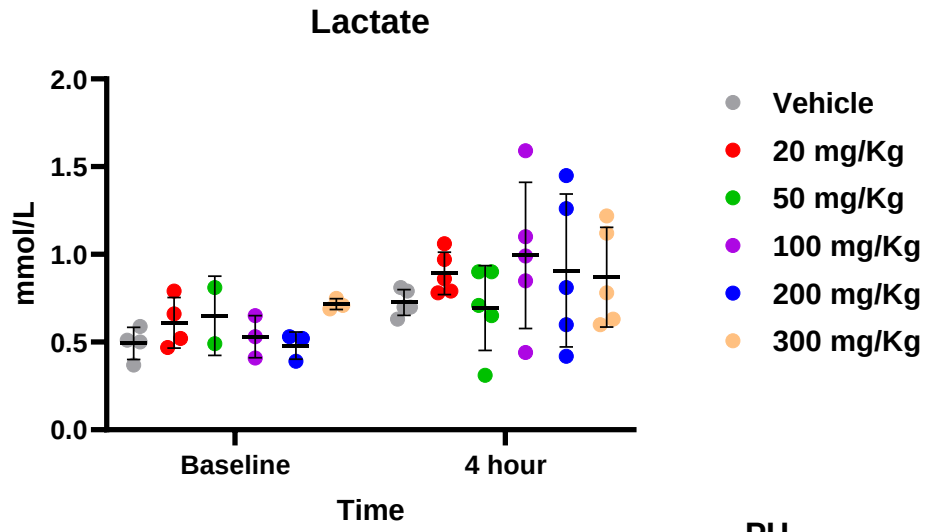
Results (Hemodynamics)

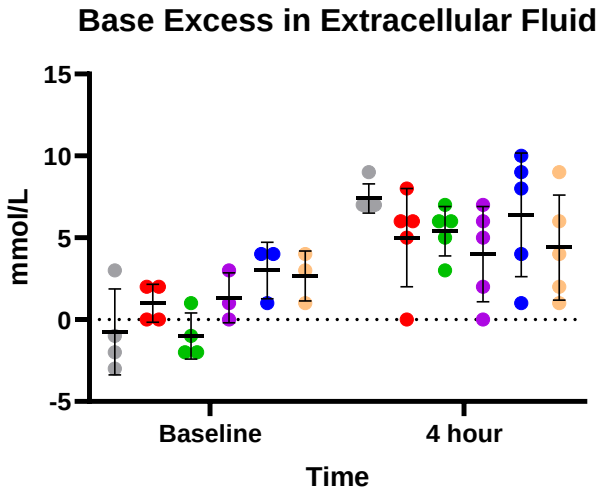


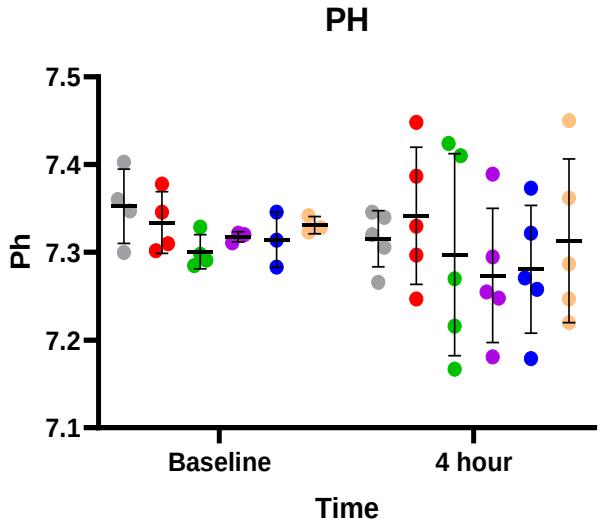


No clinically significant hemodynamic changes were observed following TXA administration

Results (Blood Gas Results)

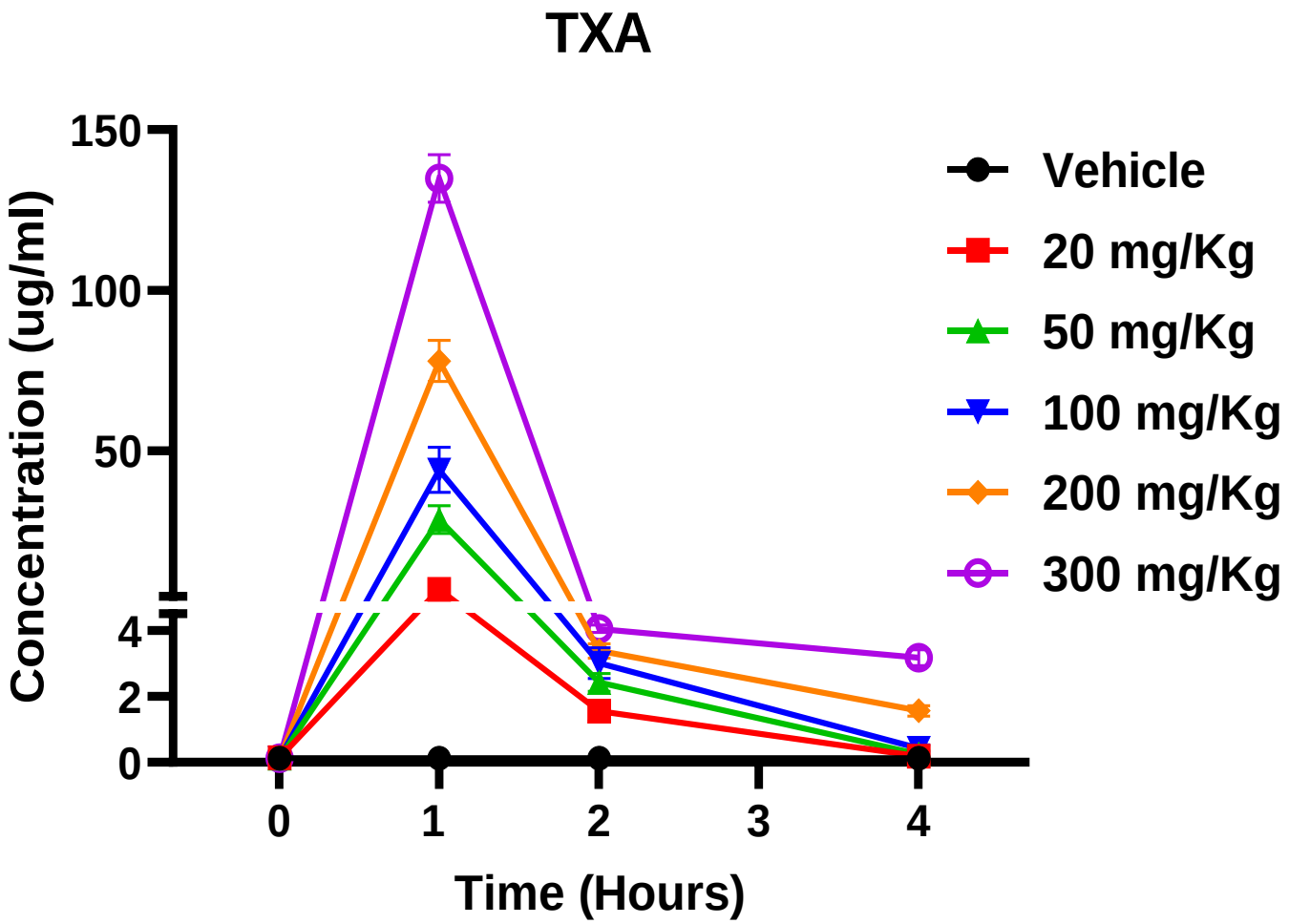


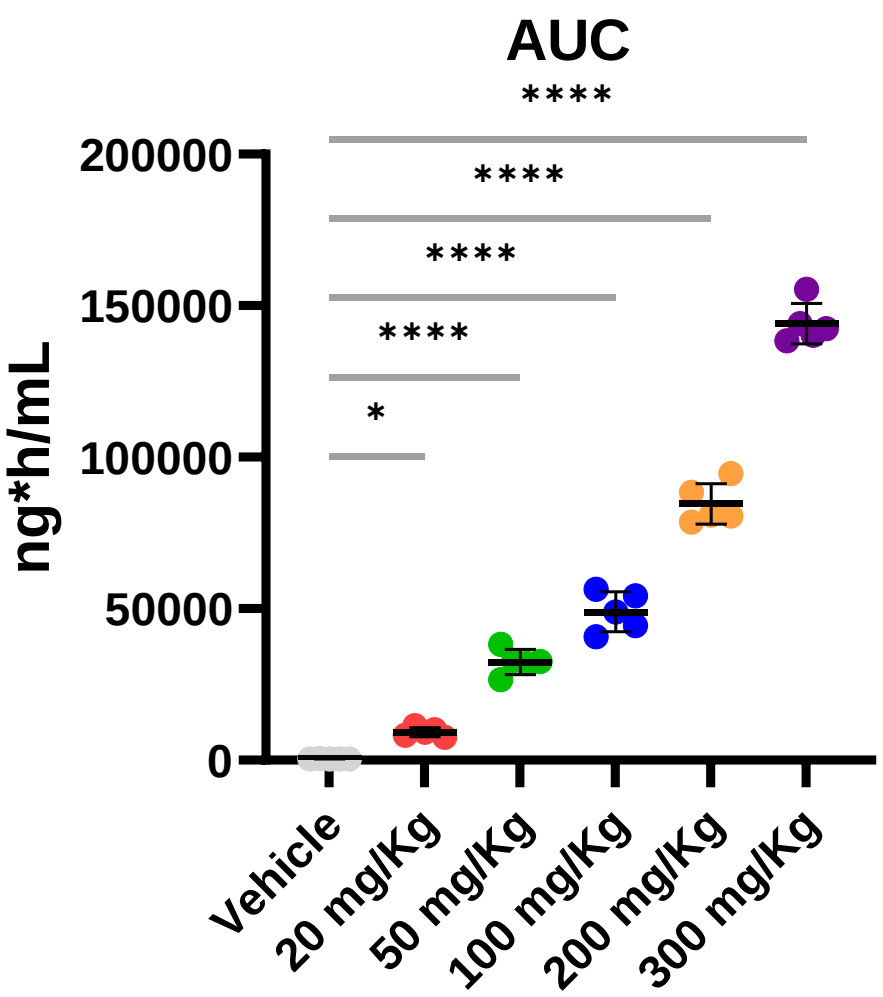




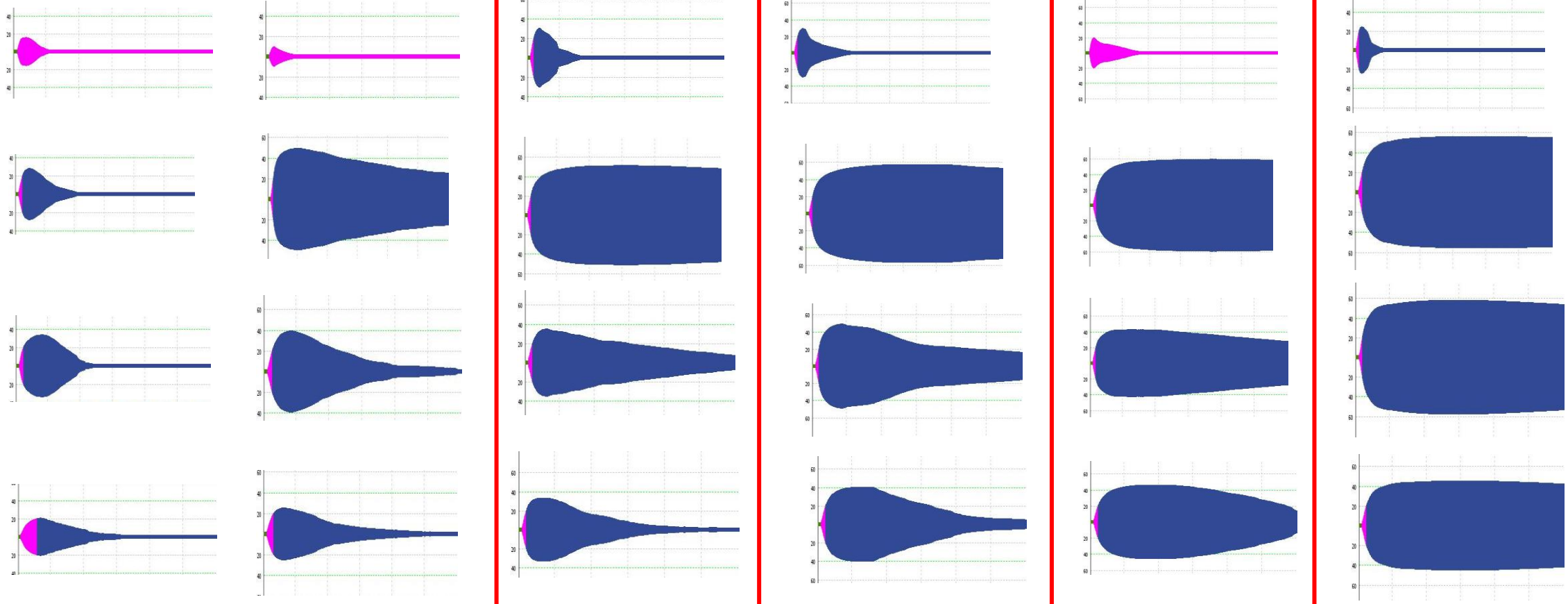
- No significant dose-dependent changes observed in pH, lactate, or base excess.
- Blood gas parameters remained within normal physiologic range.

Results - Plasma TXA Concentration

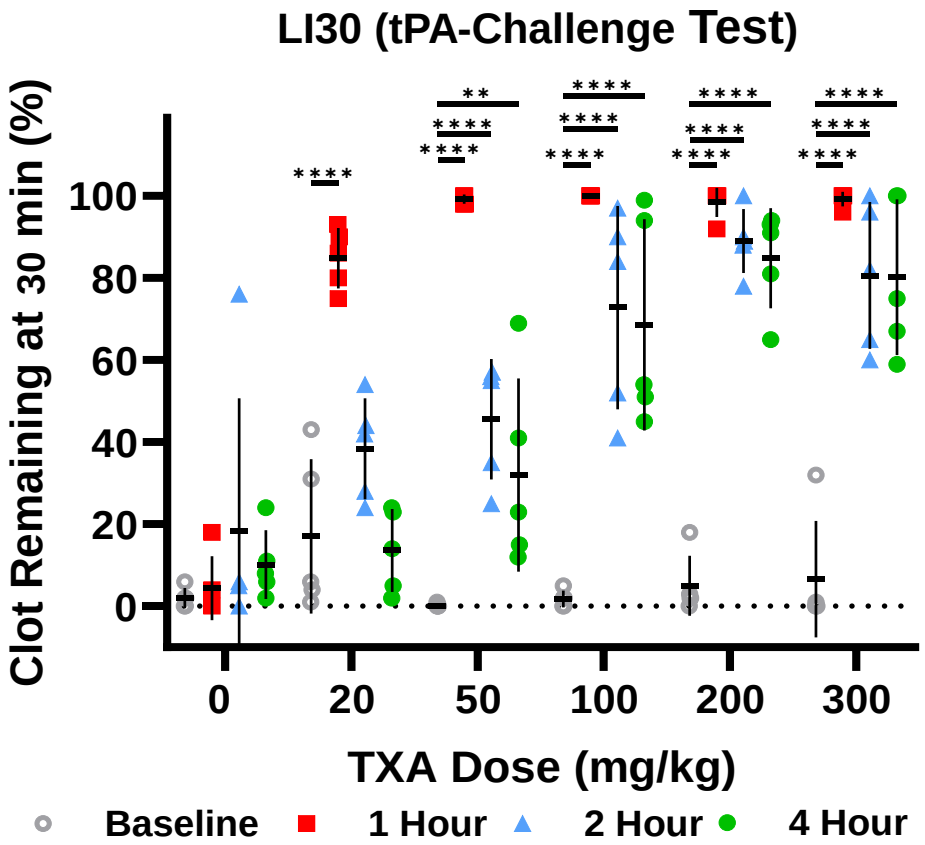


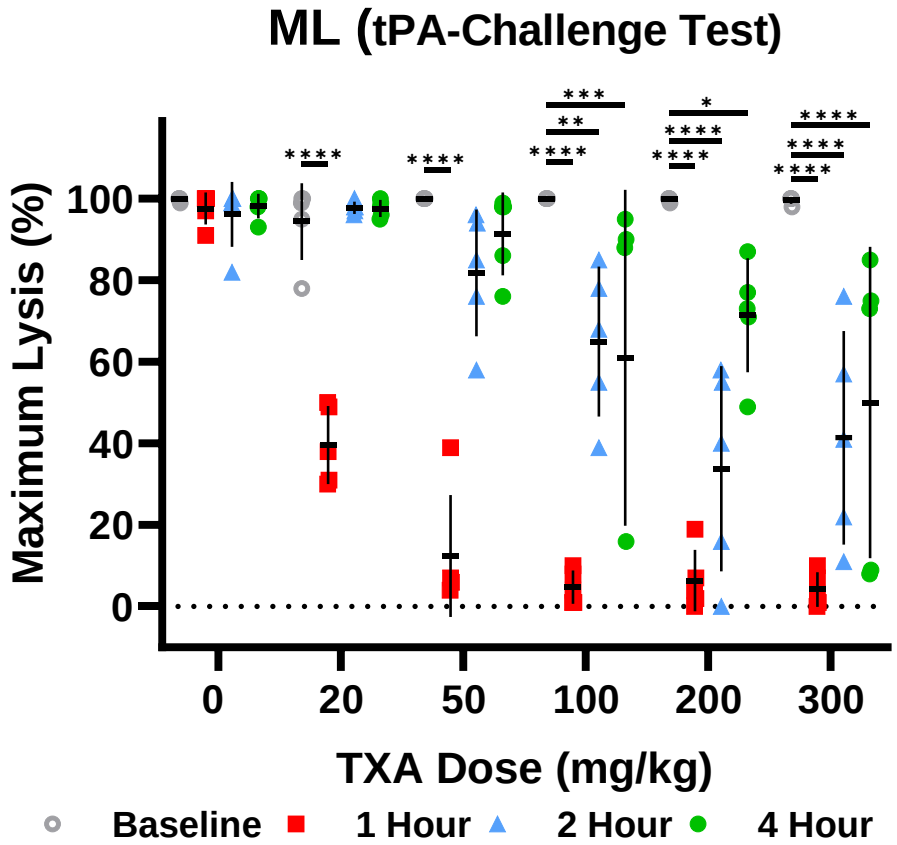


Results (tPA Challenge Test)



Results (tPA Challenge Test)





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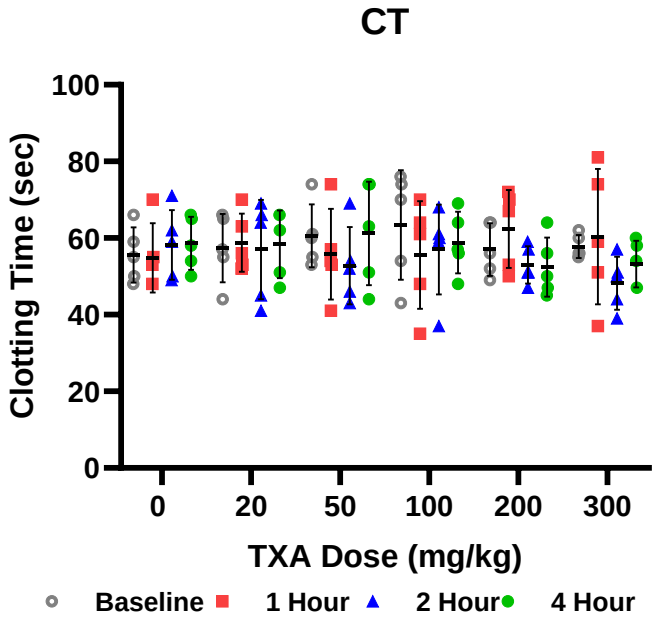

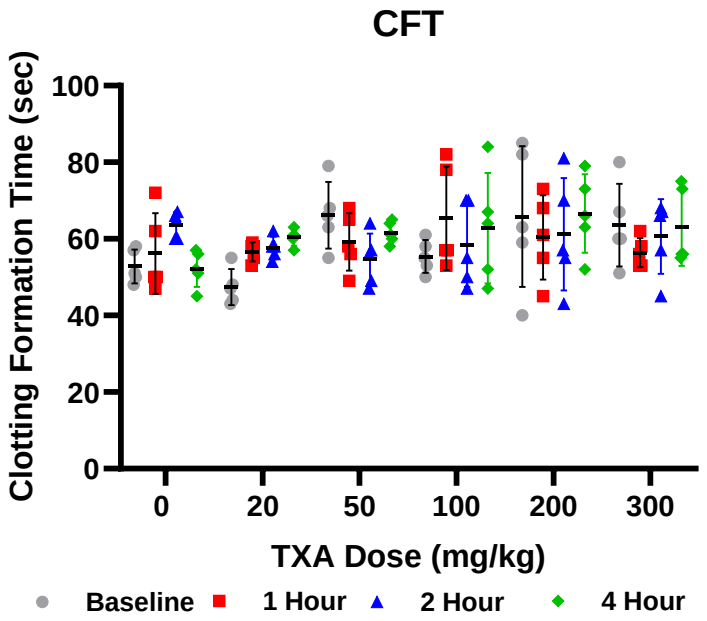

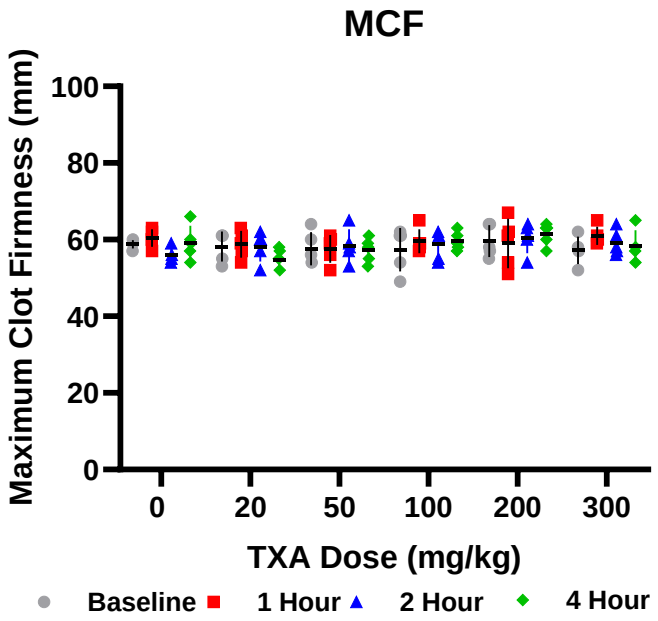

Summary/Conclusions

- TXA did not induce hypercoagulability in healthy rats.
- Peak plasma-free TXA levels occurred at 1 hour after dosing. A 50 mg/kg dose of TXA provided short-term protection from tPA-induced hyperfibrinolysis, whereas a 200 mg/kg or higher dose sustained clot preservation for at least 4 hours against a hyperfibrinolytic challenge.
- Biochemistry and hemodynamic parameters showed no significant changes from baseline post-TXA administration, and H&E tissue staining revealed no significant abnormalities.
- These findings support further studies of prophylactic TXA dosing strategies to mitigate trauma-induced coagulopathy and traumatic bleeding.

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- Samuel Knebel, M.S.
- Madeline Lawrence, B.S.
- Maegan French, PhD Student

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Questions

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