TRANEXAMIC ACID TO REDUCE TRANSFUSION IN MAJOR NON-CARDIAC SURGERY

Slides courtesy of D. Solvason (Research Manager, Winnipeg)
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TRACTION: Common Questions

Informed by Evidence

Outline

- TRACTION overview
- Review of Evidence
  - POISE-3
- Common Questions

TRACTION

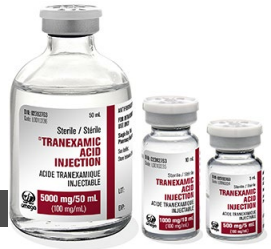
BACKGROUND

- **BLOOD:** EXPENSIVE & LIMITED RESOURCE

- Transfusions are associated with adverse patient outcomes
  - **Allergic** reactions
  - **Non-allergic** reactions
    - Infection
    - Immune dysregulation
    - Prolonged hospital length of stay
    - Increased morbidity
    - Increased mortality

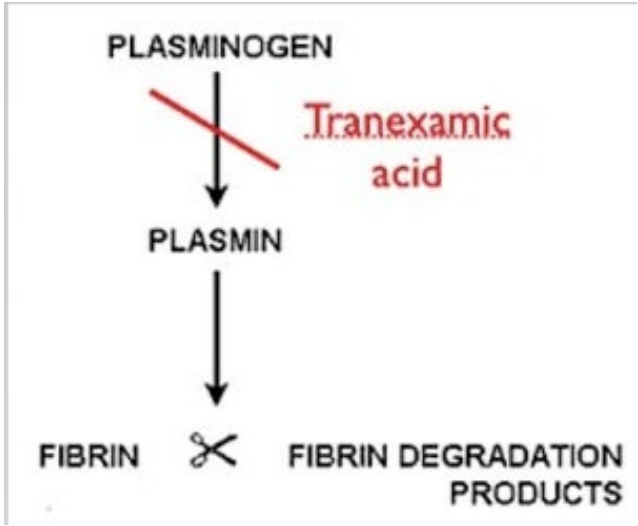
Delaney, Lancet, 2016
Carson, NEJM, 2017
Carson, JAMA, 2014

BACKGROUND – TRANEXAMIC ACID (TXA)



- **TXA** : INEXPENSIVE, WIDELY AVAILABLE, REDUCES BLEEDING

- TXA has been shown to reduce RBC transfusion
  - Trauma (CRASH-2)
  - Post-partum hemorrhage (WOMAN)
  - Cardiac surgery
  - Hip and knee arthroplasty
  - POISE-3



Levy, Anesthesiology, 2018

TXA in SURGERY

- Systematic reviews (efficacy)
  - Cochrane (mainly **ortho** and **cardiac**, n=48,000)
    - Transfusion RR 0.61, 95%CI 0.53-0.70, 18% ARR
  - *Transfus Med Review* (High risk **non-ortho/cardiac**, n=6157)
    - Transfusion RR 0.59, 95%CI 0.48-0.72, low/moderate quality
    - Reduction of 0.51 RBC units/patient (95% CI 0.13-0.90)

Montroy J, et al. The Safety and Efficacy of Lysine Analogues in Cancer Patients: A Systematic Review and Meta-Analysis. *Transfus Med Rev* 2017; **31**(3): 141-8
Henry DA,,et al. Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion. *Cochrane Database Syst Rev* 2011; (3): CD001886.

TRACTION

TXA in SURGERY

- Systematic reviews (safety)
  - **Cochrane (ortho/cardiac)**
    - No evidence of increase in VTE (RR 1.03, 95%CI 0.67-1.58)
  - **Cancer surgery (n=1075)**
    - No increase in VTE (OR 0.58, 95%CI 0.26-1.28)
  - **High risk non-ortho/non-cardiac**
    - No increase in DVT (RR 1.03, 95% CI 0.78-1.48), n = 3333
    - No increase in PE (RR 1.00, 95% CI 0.54 to 1.84), n=2469
    - **Trial sequential analysis**: no inc'd risk DVT w/ TXA

Montroy J. *Transfus Med Rev* 2017; **31**(3): 141-8

Houston BL, 2019 (Manuscript Accepted. Transfusion Medicine Reviews)

TXA in SURGERY

- Limitations:
  - No LARGESCALE studies specifically targeting safety
  - Follow up limited to in-hospital
  - **LACK of REAL-WORLD EVIDENCE**

TRACTION

RESEARCH QUESTION

Would hospital policy-level implementation of routine TXA use in surgeries at high risk of bleeding result in:

- Reduced transfusion rates?
- **Without** increase in VTE?

TRIAL DESIGN

- Multi-centre (n = 8) cluster cross over trial
- Each **site** will be randomized every 4 weeks
- Overall estimated enrollment ~ 8300 patients / 10-12 months

TRACTION

PRIMARY OUTCOMES

- Proportion of patients transfused red blood cells (RBCs)
- Incidence of venous thromboembolism (VTE) [deep vein thrombosis (DVT) or pulmonary embolism (PE)] within 3 months of surgery.

INCLUSION CRITERIA

Cluster-level inclusion criteria:

Hospital sites will be included in the trial if anesthesia and hospital leadership agree to manage patients as per the policy being implemented and evaluated in the trial.

Patient-level inclusion criteria:

- Patients >/= 18 years of age undergoing **major non-cardiac surgery**
  - **Inpatient** surgeries, with:
  - Estimated **>/= 5% risk of RBC transfusion**
  - **Open** or **laparoscopic** (if >/= 3 hours)

INCLUSION CRITERIA-Eligible Surgeries

Examples **of eligible surgeries could include (but are not limited to):**

1. General surgery (esophagectomy, gastrectomy, gastric repair, small bowel repair or resection, ostomy formation, colon/rectum repair or resection, colostomy, splenectomy, hepatectomy, pancreatectomy, resection of abdominal mass)
2. Orthopedics (hip fracture repair, pelvic fixation, femur repair / fixation, shoulder / humerus open reduction internal fixation, lower extremity amputation)
3. Spine (vertebrectomy, surgery involving >/= 3 levels)
4. Otolaryngology (glossectomy, mandibulectomy, radical laryngectomy)
5. Thoracic (lung resection or decortication)

TRACTION

INCLUSION CRITERIA-Eligible Surgeries

Examples **of eligible surgeries could include (but are not limited to):**

6. Vascular (arterial bypass / endarterectomy / aneurysmorrhaphy involving the aorta or proximal vessels off the aorta)

7. Gynecology (hysterectomy)

8. Urology (nephrectomy, cystectomy, prostatectomy, pelvic exenteration)

9. Plastic surgery (large neoplasm resections, burns or debridements)

10. Surgeries anticipated to be associated with 5% or greater risk of RBC transfusion in hospital as per the surgical team.

EXCLUSION CRITERIA

The following groups of patients will be excluded from the TRACTION trial:

1. Active thromboembolic disease
   - Patient is anticoagulated for active thromboembolic disease prior to admission ('Active' thromboembolic disease is defined as a new diagnosis, venous or arterial thrombotic event within 3 months of surgery)
   - Patients with a thrombotic event beyond 3 months prior to surgery are generally eligible for inclusion at the discretion of the medical team
2. Pregnancy
3. Cardiac surgery and hip and knee arthroplasty where TXA is standard-of-care.
4. Surgeries with free flap reconstruction
5. Trauma surgeries where TXA was administered within the previous 3 hours

- For clarification: Pre-operative use of anticoagulants or antiplatelet agents (single or dual antiplatet therapy) for reasons other than active thrombosis (ie. chronic venous thrombosis, atrial fibrillation, peripheral vascular disease, etc) are **NOT** reasons for exclusion from the trial.

TRACTION: Common Questions

TRACTION vs POISE-3. What's the difference?

My patient has CVS risk factors. What now?

Why THIS surgery?

Why this consent model?

TXA: Review of Evidence

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Tranexamic Acid in Patients Undergoing Noncardiac Surgery

P.J. Devereaux, M. Marcucci, T.W. Painter, D. Conen, V. Lomivorotov, D.I. Sessler, M.T.V. Chan, F.K. Borges, M.J. Martínez-Zapata, C.Y. Wang, D. Xavier, S.N. Ofori, M.K. Wang, S. Efremov, G. Landoni, Y.V. Kleinlugtenbelt, W. Szczeklik, D. Schmartz, A.X. Garg, T.G. Short, M. Wittmann, C.S. Meyhoff, M. Amir, D. Torres, A. Patel, E. Duceppe, K. Ruetzler, J.L. Parlow, V. Tandon, E. Fleischmann, C.A. Polanczyk, A. Lamy, S.V. Astrakov, M. Rao, W.K.K. Wu, K. Bhatt, M. de Nadal, V.V. Likhvantsev, P. Paniagua, H.J. Aguado, R.P. Whitlock, M.H. McGillion, M. Prystajecky, J. Vincent, J. Eikelboom, I. Copland, K. Balasubramanian, A. Turan, S.I. Bangdiwala, D. Stillo, P.L. Gross, T. Cafaro, P. Alfonsi, P.S. Roshanov, E.P. Belley-Côté, J. Spence, T. Richards, T. VanHelder, W. McIntyre, G. Guyatt, S. Yusuf, and K. Leslie, for the POISE-3 Investigators*

N ENGL J MED 386;21 NEJM.ORG MAY 26, 2022

POISE-3

Clinical Question

- In patients undergoing **noncardiac surgery** who are at **risk of bleeding and cardiovascular events**, does TXA lower the risk of bleeding while being noninferior to placebo with regards to cardiovascular complications, at 30 days?

POISE-3

- Multicentre, double-blind, RCT
- N = 9535, 114 sites, 22 countries
- Intervention: 1 gram TXA x2
- Follow-up: 30 days
- Primary Outcomes:
  - Efficacy: composite BLEEDING *(life-threatening, major, or bleeding into a critical organ)*
  - Safety: composite CVS *(MI, TnI, CVA, periph arterial thrombosis or venous thromboembolism)*

POISE-3

Hypothesis → EFFICACY

TXA is superior to placebo wrt composite bleeding outcome

Hypothesis → SAFETY

TXA is NON-INFERIOR to placebo wrt to composite cardiovascular outcome

i.e.

"TXA is NOT WORSE than placebo"

POISE-3: POPULATION

INCLUSION

- Age > 45 yrs
- Inpatient noncardiac surgery
- Risk of bleeding
- Risk of CVS complications

EXCLUSION

- Cardiac or intracranial surgery
- Planned administration of TXA
- eGFR < 30 mL/min
- Longterm dialysis

Baseline Characteristics

Characteristics	Tranexamic Acid (N=4757)	Placebo (N=4778)
Age — yr	69.5±9.5	69.3±9.4
Male sex — no./total no. (%)	2669/4755 (56.1)	2681/4778 (56.1)
Eligibility criteria met — no. (%)	4742 (99.7)	4766 (99.7)
NT-proBNP ≥200 ng/liter	574 (12.1)	552 (11.6)
History of coronary artery disease	1410 (29.6)	1466 (30.7)
History of peripheral artery disease	714 (15.0)	722 (15.1)
History of stroke	400 (8.4)	388 (8.1)
Undergoing major vascular surgery	541 (11.4)	544 (11.4)
Risk criteria		
Met ≥3 of 9 criteria	3988 (83.8)	4003 (83.8)
Undergoing major surgery†	3741 (78.6)	3798 (79.5)
Undergoing urgent or emergency surgery	555 (11.7)	540 (11.3)
Age ≥70 yr	2611 (54.9)	2588 (54.2)
Current diabetes for which medication is taken	1749 (36.8)	1812 (37.9)
Preoperative serum creatinine level >175 μmol/liter	57 (1.2)	73 (1.5)
History of congestive heart failure	674 (14.2)	671 (14.0)
History of transient ischemic attack	282 (5.9)	247 (5.2)
History of hypertension	4293 (90.2)	4321 (90.4)
History of smoking within 2 yr before surgery	1131 (23.8)	1128 (23.6)
Other medical history — no. (%)		
Atrial fibrillation	478 (10.0)	445 (9.3)
Active cancer	1311 (27.6)	1360 (28.5)

Baseline Characteristics

Surgery — no./total no. (%)		
Any procedure	4729/4757 (99.4)	4740/4778 (99.2)
General‡	1769/4729 (37.4)	1773/4740 (37.4)
Orthopedic	1083/4729 (22.9)	1063/4740 (22.4)
Vascular	699/4729 (14.8)	700/4740 (14.8)
Urologic	598/4729 (12.6)	624/4740 (13.2)
Spinal	237/4729 (5.0)	206/4740 (4.3)
Gynecologic	162/4729 (3.4)	171/4740 (3.6)
Thoracic	127/4729 (2.7)	146/4740 (3.1)
Low-risk	39/4729 (0.8)	34/4740 (0.7)
Plastic	14/4729 (0.3)	23/4740 (0.5)

POISE-3: OUTCOMES

Table 2. Effects of Tranexamic Acid on 30-Day Outcomes.*

Outcome	Tranexamic Acid (N=4757)	Placebo (N=4778)	Hazard Ratio (95% CI)†	P Value
Primary efficacy outcome: composite bleeding outcome — no. (%)‡	43[illegible] (9.1)	561 (11.7)	0.76 (0.67–0.87)	<0.001§
Individual components of composite bleeding outcome — no. (%)				
Life-threatening bleeding¶	78 (1.6)	79 (1.7)	0.99 (0.73–1.36)	
Major bleeding¶	363 (7.6)	496 (10.4)	0.72 (0.63–0.83)	
Bleeding into a critical organ¶	12 (0.3)	21 (0.4)	0.57 (0.28–1.16)	
Primary safety outcome: composite cardiovascular outcome — no./total no. (%)‖	649/4581 (14.2)	639/4601 (13.9)	1.02 (0.92–1.14)	0.04**

Outcomes: Summary

BLEEDING OUTCOME

- **9.2%** (TXA) *vs* **11.7%** (placebo)
- Absolute difference: - 2.6%
- P < 0.001, HR 0.76 (0.67-0.87)

1. Bleeding is COMMON
2. TXA SIGNIFICANTLY reduces bleeding vs placebo

Outcomes: Summary

CARDIOVASCULAR OUTCOMES

- **649**/4581events (TXA)- **14.2%**
- **639**/4601 events (placebo)- **13.9%**
- Absolute difference: **0.3%**
- HR 1.02 (0.92-1.14)
  - Noninferiority threshold < 1.125

1. Non-inferiority NOT established →
   Cannot say that TXA is "not worse" than placebo
2. Absolute difference VERY small despite high risk population
3. ? Stringent non-inferiority threshold

Common Qs: TRACTION vs POISE-3?

TRACTION

INCLUSION:

- Age ≥ 18 yrs
- Inpatient, non-cardiac surgery
  - Estimated transfusion risk ≥ 5%
  - Open, or Laparoscopic ≥ 3 hrs

"ALL COMERS"

Exclusion:

- Active thromboembolic disease
- Pregnancy
- Surgery where TXA is standard of care
- TXA within 3 hrs

POISE-3

INCLUSION:

- Age ≥ 45 yrs
- Inpatient, non-cardiac surgery
- Risk factors for of bleeding
- Risk factors for CVS complications

"HIGH-RISKERS"

Exclusion:

- Cardiac or intracranial surgery
- Planned TXA administration
- eGFR < 30 ml/min
- Longterm dialysis

Common Qs: My patient has IHD- what now?

- POISE-3 demographic → HIGH RISK for CVS complications
- N = 9500
- Non-inferiority for composite CVS outcome NOT met
- Absolute risk: **0.3%**
  - 649/4581; 14.2% (TXA) *vs*
  - 639/4601; 13.9% (placebo)

CLINICAL JUDGEMENT: RISK *vs* BENEFIT

- Surgical transfusion accounts for 40% of product use
- Serious perioperative bleeding is (surprisingly) common (> 11%)

Common Questions: Why THIS Surgery?

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Evaluation of Transfusion Practices in Noncardiac Surgeries at High Risk for Red Blood Cell Transfusion: A Retrospective Cohort Study

Brett L. Houston [a,b,*], Dean A. Fergusson [c,d], Jamie Falk [b], Emily Krupka [e], Iris Perelman [c], Rodney H. Breau [c,f], Daniel I McIsaac [c,g], Emily Rimmer [a], Donald S. Houston [a], Allan Garland [h], Robert E. Ariano [b], Alan Tinmouth [c,d], Robert Balshaw [i], Alexis F. Turgeon [j,k], Eric Jacobsohn [l], Jason Park [m], Gordon Buduhan [m,n], Michael Johnson [m], Joshua Koulack [m], Ryan Zarychanski [a,n]

Common Questions: Why MY surgery?

- Retrospective cohort study (2014-2016)
- Describe transfusion practices in noncardiac surgeries at “high risk of blood transfusion”
- 5 tertiary care hospitals (Winnipeg-3; Ottawa-2) + NSQUIP
- Identified 95 non-cardiac surgeries at ≥ 5% risk transfusion, representing 28,116 patient admissions (Canada)
- **16% baseline transfusion** risk (range 5-49%)
- TXA used in only **13.3%** of surgeries (mostly orthopedic)

Common Questions: Why Waived Consent?

- TRACTION trial is a **MINIMAL RISK TRIAL**
  - > 50,000 patients randomized to receive TXA vs placebo in trauma, PPH, head injury, cardiac surgery, or non-cardiac surgery, no evidence of increased thrombosis or other events suggesting risk of harm
- Both interventions fall within **USUAL CARE**
  - patients undergoing high-risk surgery currently may or may not receive TXA at discretion of anesthesiologist
- Consent model informed by **extensive discussion** with **patient-partners & stakeholders**
- Fulfills all items relevant to "Alterations to Consent Requirements" of Tri-Council Policy Statement (TCPS-2): Ethical Conduct for Research Involving Humans