DEPOSITION

Topical Tranexamic Acid to Reduce Seizures in Cardiac Surgery

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Funding: Canadian Institutes of Health Research

Population Health Research Institute
HEALTH THROUGH KNOWLEDGE

Disclosure

- None

Background

- Perioperative bleeding in cardiac surgery is associated with morbidity and mortality
- IV antifibrinolytics are standard of care: tranexamic acid (TxA)
- IV TxA increases the risk of seizure

Problem

- Anesthesiologists decrease the dose of TxA to prevent seizures
- It may increase the risk of bleeding
- Giving TxA directly on the source of bleeding (topical) has been tested in various type of surgery
- Promising alternative in our pilot study

Question

- In patients undergoing on-pump cardiac surgery, does topical tranexamic acid (intra-pericardial) compared to the usual intravenous tranexamic acid administration

  -reduce the risk of in-hospital seizure without increasing red blood cell transfusion?

Design

- Randomized controlled trial
- Double dummy to maintain blinding
  - Each patient received 2 syringes (up to 10g) for intravenous use and 2 syringes (up to 10g) for topical use
  - Investigator initiated trial
- Sample size: 3800 patients
- Funding: Canadian Institute of Health Research

Eligibility criteria

- Included patients
  - ≥18 yrs undergoing cardiac surgery with cardiopulmonary bypass
  - Median sternotomy
- Excluded patients (too low or too high risk of bleeding)
  - Minimally invasive surgery or off-pump CABG
  - Bleeding disorder
  - eGFR <30 ml/min
  - Pre-operative hemoglobin >170 g/L or <110 g/L or thrombocytopenia (<50,000 platelets per µL)
  - Expected circulatory arrest
  - Active endocarditis

Intervention and Follow-up

- Patients randomized to receive
  - TXA 1-10 g IV bolus or placebo at start and during surgery
  - TXA 1-10 g topical or placebo at end of surgery (Protamine)

- Follow-up
  - until discharge or 10 days, whichever occurred first

Outcomes

- Primary outcome
  - Seizure
- Secondary outcome
  - Red blood cell transfusion
- Tertiary outcomes: blood products transfusion, composite (death, MI, stroke), reoperation for bleeding or tamponade, ICU length of stay

Statistics

- Primary outcome hypothesis
  - Topical TXA superior to IV TXA for seizure
  - Fisher's exact test with 2-sided P <0.05
- Secondary outcome hypothesis
  - Topical TXA noninferior to IV TXA for red blood cell transfusion
    - upper bound of 1-sided 97.5% CI for HR needed to fall below 1.15
    - 1-sided P <0.025

Enrollment

- Second pre-specified interim analysis by DSMB (75%)
- DSMB recommended to stop the trial for safety
- Operations Committee reviewed the data and stop enrollment in the trial on November 28,2023
- 3242 patients enrolled out of 3800

Baseline characteristics

Characteristics	Topical TXA (N=1624)	Intravenous TXA (N=1618)
Age – (mean yrs)	66.3	65.7
Male	77%	78%
History of		
Myocardial infarction	38%	40%
Diabetes	30%	29%
Stroke	4%	4%
Seizure history	0.9%	0.4%
Elective surgery	65%	64%

Surgical characteristics

Characteristics	Topical TXA (N=1624)	Intravenous TXA (N=1618)
CABG only	69%	70%
Valve only	13%	12%
Ascending aorta only	1%	1%
Mixed	16%	15%
Cardio-pulmonary bypass time (mins)	88.7	88.6
Cross-clamp time (mins)	66.2	66.0

Compliance and Follow-up

- In both TXA and placebo groups
  - 96.5% of patients received active treatment allocation

- Follow-up: 100% of participants completed

Primary outcome

Outcome	Topical TXA n=1624 no. (%)	Intravenous TXA n=1618 no. (%)	RR (95% CI)	P value
Seizure	4 (0.2)	11 (0.7)	0.36 (0.12-1.14)	0.07

- Fisher's exact test

Post Hoc Primary outcome

Outcome	Topical TXA n=1624 no. (%)	Intravenous TXA n=1618 no. (%)	RR (95% CI)	P Value¶
Seizure*	4 (0.2)	11 (0.7)	0.36 (0.12-1.14)	0.07
Any seizure	4 (0.2)	14 (0.9)	0.29 (0.09-0.86)	0.02

*patients with seizure and stroke were excluded

¶ Fisher's exact test

Post Hoc Primary outcome

Outcome Stroke	Topical N=22 no. (%)	Intravenous n=12 no. (%)	RR (95% CI)	P value
Any seizure	0 (0)	3 (25%)	-	0.04

- Fisher's exact test

Post Hoc Primary outcome

Outcome	Close chambers n=2268 no. (%)	Open chambers n=940 no. (%)	RR (95% CI)	P value
Seizure	7 (0.3)	8 (0.9)	0.36 (0.13-0.99)	0.04
Any seizure	8 (0.4)	10 (1.1)	0.33 (0.13-0.84)	0.01

- Chi-square

Secondary outcome

Outcome	Topical TXA n=1624 no. (%)	Intravenous TXA n=1618 no. (%)	RR (95% CI)	P value
RBC transfusion	570 (35.1)	433 (26.8)	1.31 (1.18-1.46)	< 0.001

One-side value for non-inferiority P=0.007

Tertiary outcome

Outcome	Topical TXA n=1624 no. (%)	Intravenous TXA n=1618 no. (%)	RR (95% CI)
Any blood products	756 (46.6)	583 (36.0)	1.29 (1.19-1.40)
Reoperation bleeding	63 (3.9)	46 (2.8)	1.37 (0.94-1.98)
ICU LOS (hr) –median	24	24	-
MACE	40 (2.5)	31 (1.9)	1.29 (0.81-2.04)

Post Hoc Tertiary outcome

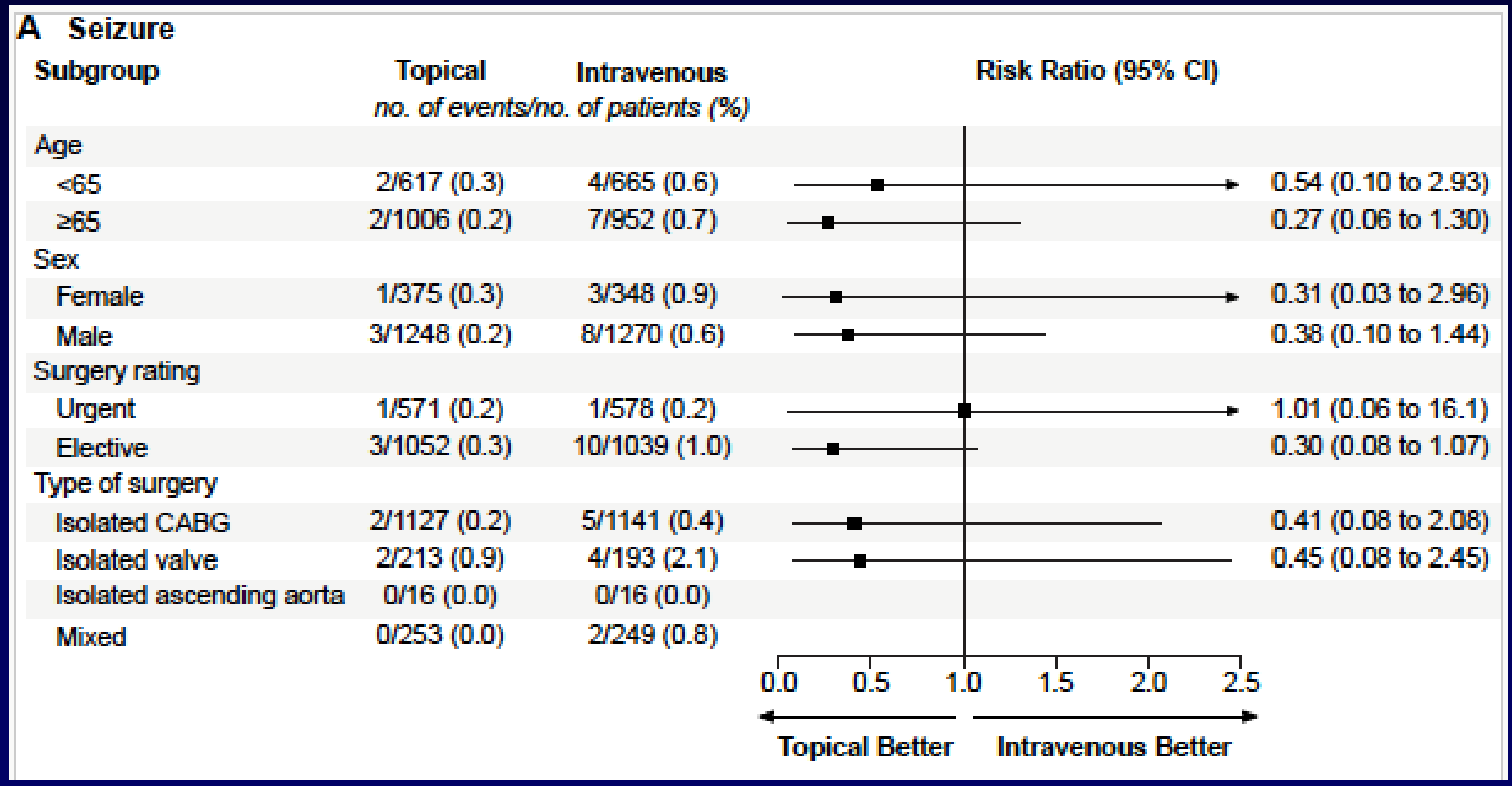
Outcome	Topical TXA n=1618 no. (%)	Intravenous TXA n=1608 no. (%)	RR (95% CI)	P value	P value *
KDIGO stage 1	322 (19.9)	330 (20.5)	0.95 (0.92-0.99)	0.02	0.45
KDIGO stage 2	7 (0.4)	5 (0.3)	1.37 (0.44-4.27)	0.59	0.51
KDIGO stage 3	24(1.5)	10 (0.6)	2.35 (1.14-4.83)	0.02	0.12
Dialysis	19 (1.2)	6 (0.4)	3.16 (1.26-7.88)	0.01	0.05

* Controlled for bleeding

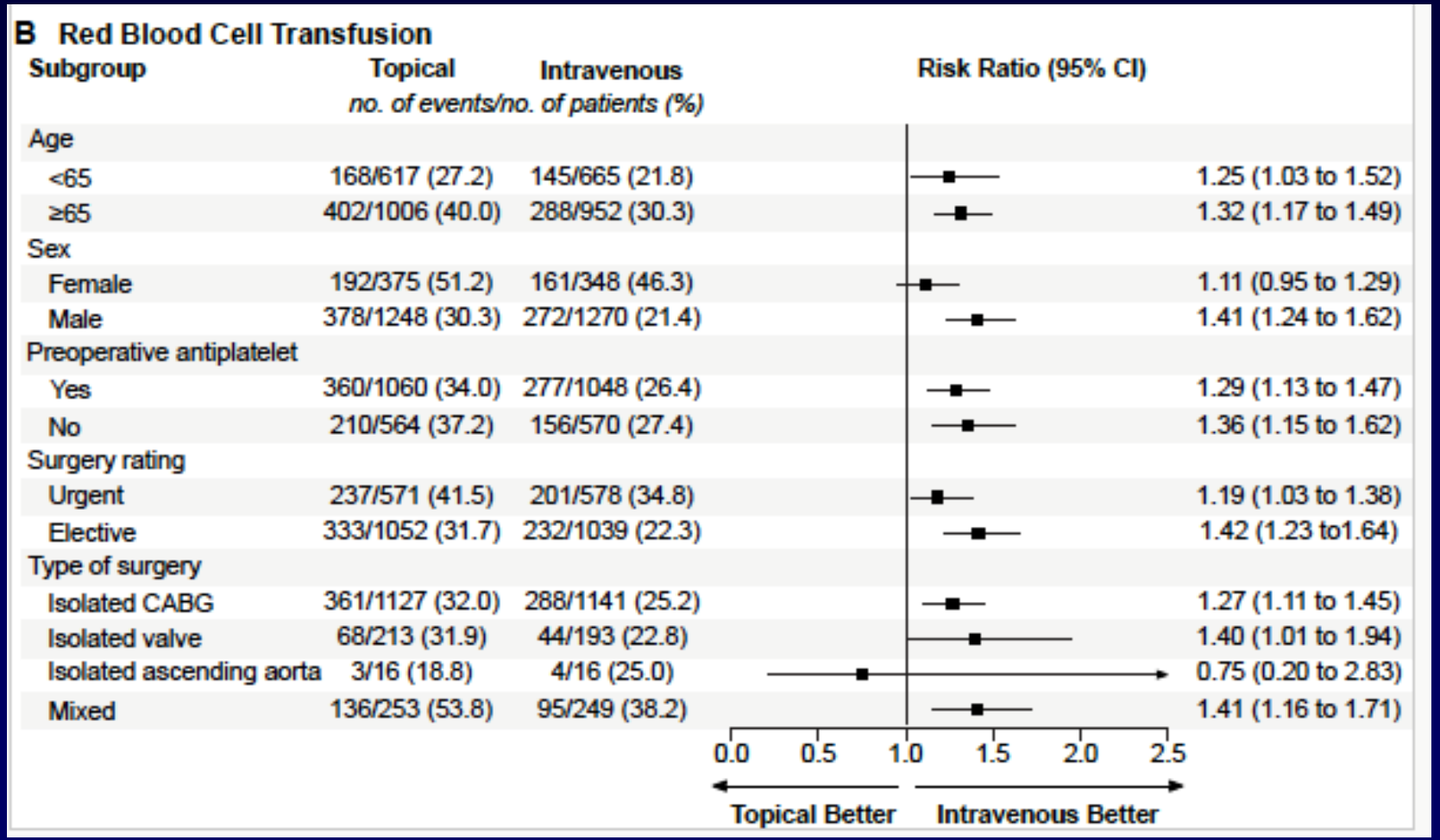
Intravenous dosage and Outcomes

Intravenous TXA n=1618 no. (%)	Group n=	Seizure no. (%)	Any Seizure no. (%)	RBC transfusion no. (%)
0 to 36mg/kg	612	5 (0.8)	5 (0.8)	164 (26.8)
36.1 to 60mg/kg	621	4 (0.6)	5 (0.8)	154 (24.8)
>60.1 mg/kg	355	2 (0.6)	4 (1.1)	110 (31.0)

Subgroup Seizure



Subgroup RBC transfusion

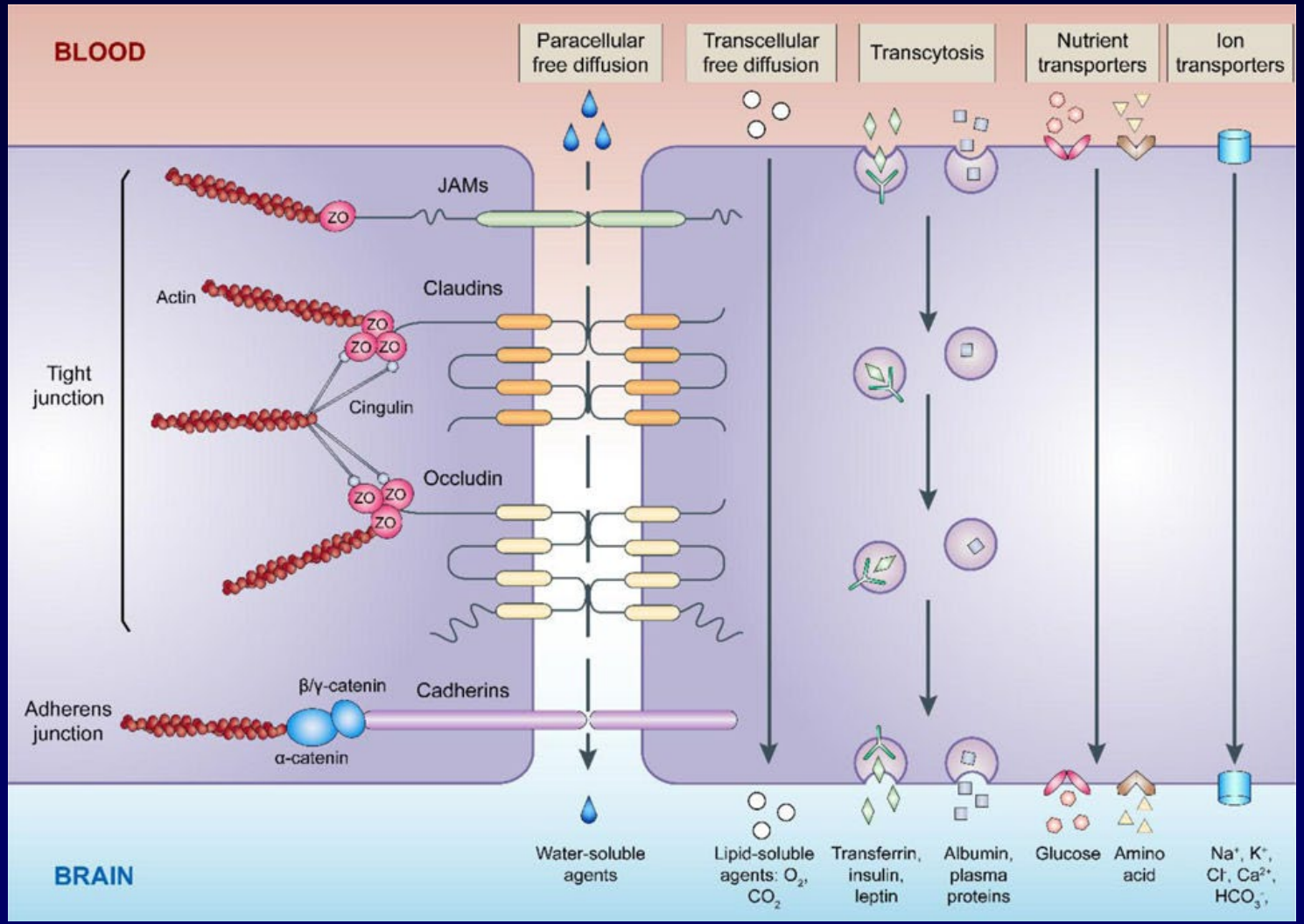


Conclusions of our trial

Topical vs. Intravenous TXA cardiac surgery

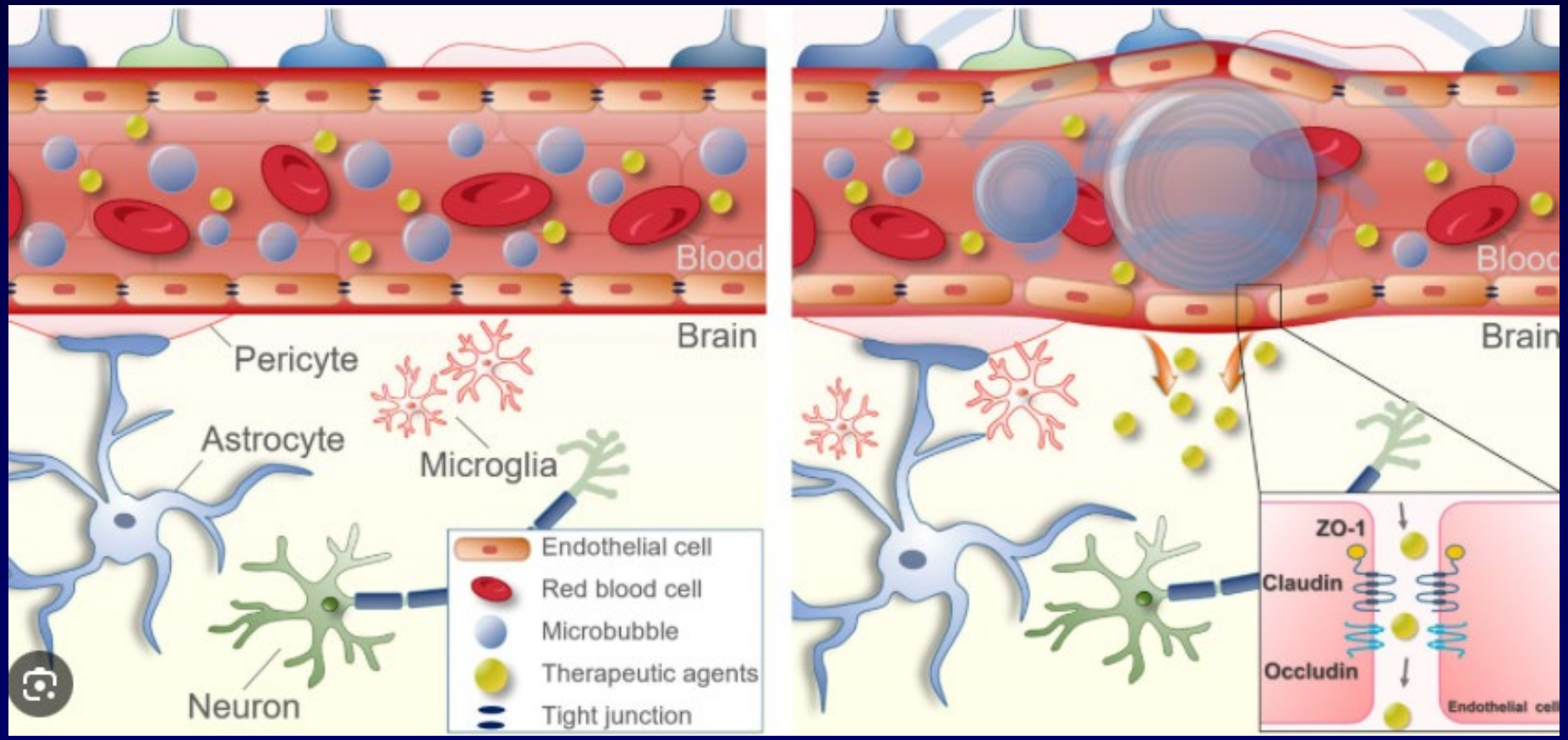
- Topical TXA does not reduce risk of seizure
- Topical TXA increases the risk of transfusion

How does TxA cross the blood-brain barrier?



Jiang X, et al. Prog Neurobiol. 2018

Micro-bubbles and Focused ultrasound

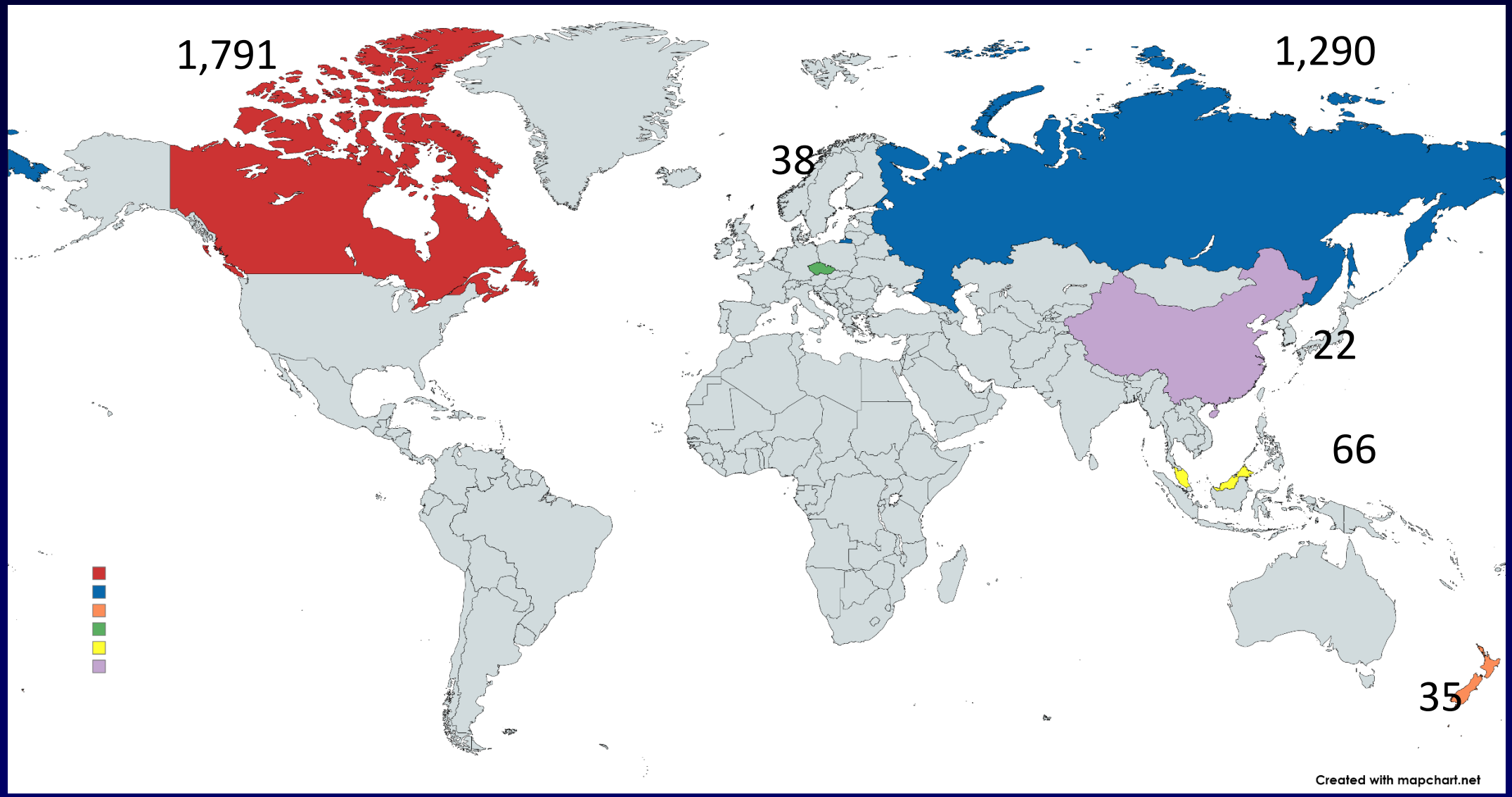


Further hypotheses

- Mechanism of seizure is more complex
  - Not only related to dose of IV TxA
  - Probably mediated by embolism of air or debris
  - Presence or absence of TxA at the time of embolism could be the mechanism: timing
  - Easily available tests for TxA levels are needed

- Thank you.

3242 patients randomized
16 centres in 6 countries



Glycine receptors

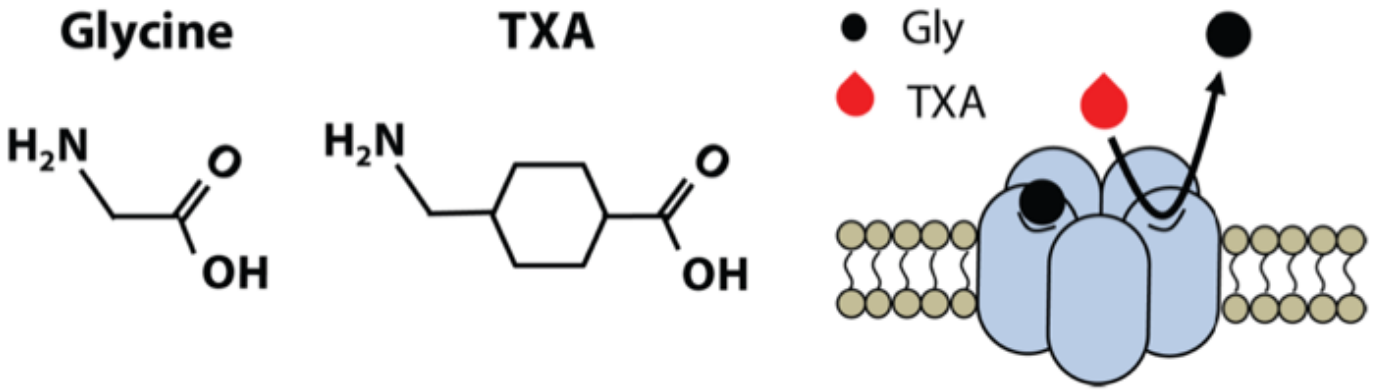
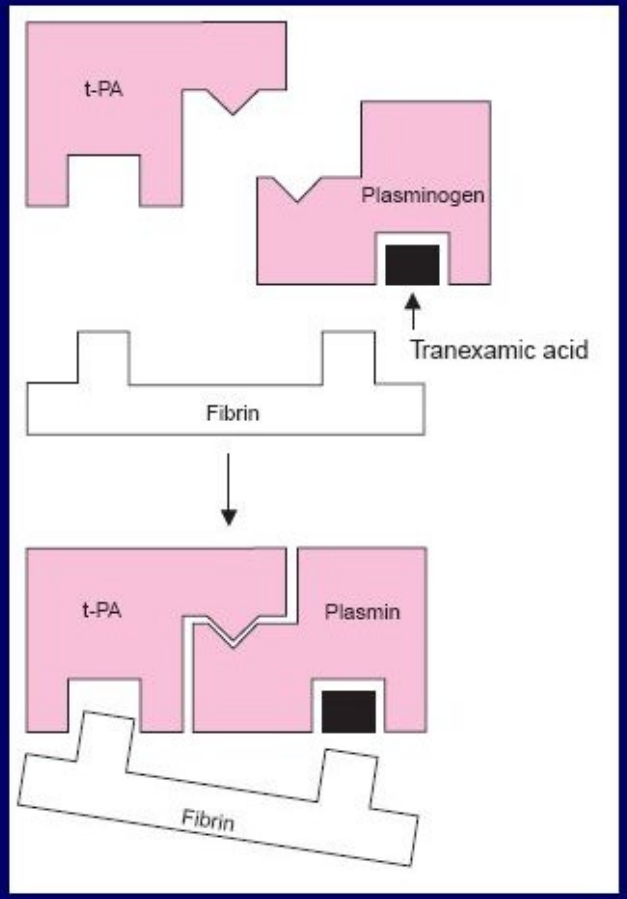


Figure 2.4 TXA is a competitive antagonist of glycine receptors.

Glycine and TXA are structural analogues suggesting that TXA competes for the glycine binding site of the glycine receptor.

Tranexamic acid and bleeding



- **Tranexamic Acid (TXA)** is a synthetic derivative of the amino acid lysine.
  - It has a very high affinity for the lysine binding sites of plasminogen.
  - It blocks these sites and prevents binding of plasmin to the fibrin surface, thus exerting its antifibrinolytic effect.