When Should I Use Tranexamic Acid for Children?

Dr Andrea Kelleher

Consultant Adult and Paediatric Cardiac Anaesthetist

When?

* When a drug is licenced for (the proposed) use
* When its use is supported by expert opinion
* When I understand which of my patients will benefit
* When I understand the side effects and contraindications
* When I know what dose to give
* When I understand the timing of administration

BNF For Children - TXA

* Licenced Uses:
  * Excessive fibrinolysis
  * Hereditary angioedema
  * Prevention of excessive bleeding following dental extraction (e.g. in haemophilia)
  * Menorrhagia, traumatic hyphema and epistaxis
  * Thrombolytic overdose
  * Cardiac surgery

BNF For Children - TXA

Not licenced for:

* reduction of blood loss during cardiac surgery
* Injection not licenced use in children under 1 year
* Injection not licenced for administration by intravenous infusion

NICE Guidance

* Consider tranexamic acid for children undergoing surgery who are expected to have at least moderate blood loss (greater than 10% blood volume).

NICE guideline [NG24] Blood Transfusion November 2015

NICE National Institute for Health and Care Excellence

World Health Organisation Model List of Essential Medicines

* "The **core list** presents a list of minimum medicine needs for a basic health-care system, listing the most efficacious, safe and cost–effective medicines for priority conditions. Priority conditions are selected on the basis of current and estimated future public health relevance, and potential for safe and cost-effective treatment".

10.2 Medicines affecting coagulation	
Enoxaparin	20mg/0.2ml; 40mg/0.4ml; 60mg/0.6ml; 80mg/0.8ml/100mg/1ml; 120ml/0.8ml; 150mg/1ml
Heparin sodium	Injection: 1000IU/ml; 5000IU/ml; 20,000iu/ml in 1 ml ampoule
Phytomenadione	Injection: 1mg/ml;10mg/ml in 5ml ampoule
Protamine sulphate	Injection: 10mg/ml in 5ml ampoule
Tranexamic acid	Injection: 100mg/ml in 10ml ampoule
Warfarin	Tablet: 1mg; 2mg; 5mg

19th WHO Model List of Essential Medicines (April 2015)

bjh guidelines

Guidelines on transfusion for fetuses, neonates and older children

Helen V. New,[1,2] Jennifer Berryman,[3] Paula H. B. Bolton-Maggs,[4] Carol Cantwell,[2] Elizabeth A. Chalmers,[5] Tony Davies,[6] Ruth Gottstein,[7] Andrea Kelleher,[8] Sailesh Kumar,[9] Sarah L. Morley[10] and Simon J. Stanworth,[11] on behalf of the British Committee for Standards in Haematology

[1]NHS Blood and Transplant, [2]Imperial College Healthcare NHS Trust, London, [3]University College Hospitals NHS Trust, London, [4]Serious Hazards of Transfusion, NHS Blood and Transplant, Manchester, [5]Royal Hospital for Sick Children, Glasgow, [6]NHS Blood and Transplant, [7]St. Mary's Hospital, Manchester/University of Manchester, Manchester, [8]Royal Brompton Hospital, London, UK, [9]Mater Research Institute, University of Queensland, Brisbane, Australia, [10]Addenbrookes Hospital/NHS Blood and Transplant, Cambridge, and [11]Oxford University Hospitals NHS Trust/NHS Blood and Transplant, Oxford, UK

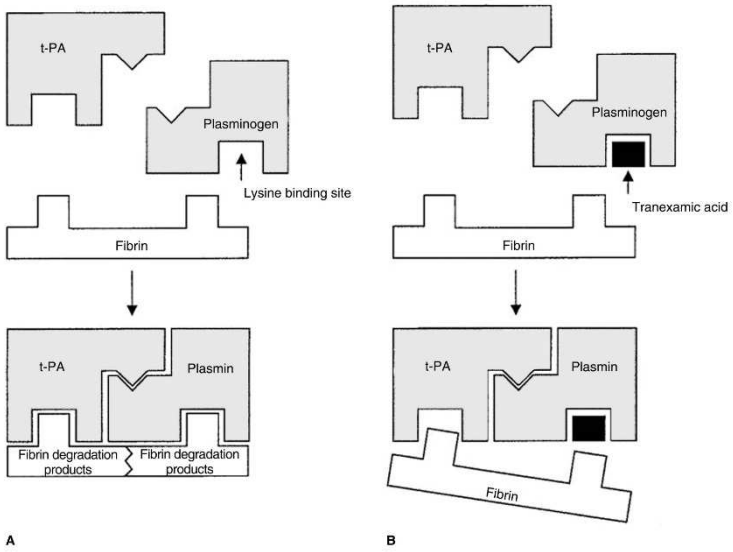
Recommendations for Tranexamic Acid:

* Tranexamic acid should be considered in all children undergoing (non-cardiac) surgery where there is risk of significant bleeding (1B).

* Consider using antifibrinolytic therapy in neonates and children undergoing cardiac surgery at high risk of significant bleeding (1B).

Tranexamic Acid

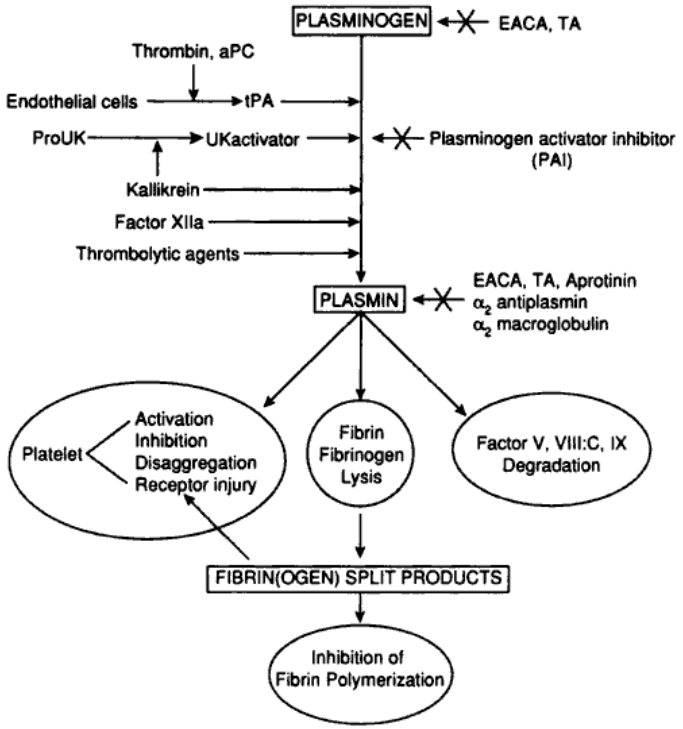
* A lysine analogue
* Inhibits plasmin mediated fibrinolysis at low doses by forming a reversible complex with plasminogen



Tranexamic Acid

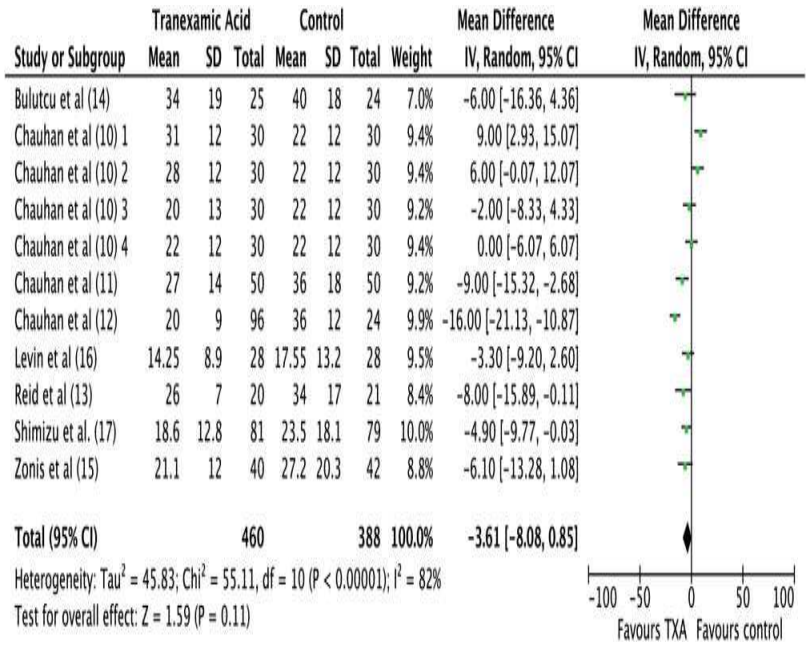
At higher concentrations tranexamic acid also:

- Non-competitively blocks plasmin
- Inhibits thrombin activation of platelets by plasmin-TXA binding to platelet receptors
- Blocks plasmin dependent complement pathway interactions
- Promotes thrombin generation via activation of factor XII



Tranexamic Acid and Paediatric Cardiac Surgery

* Blood Loss mls/kg

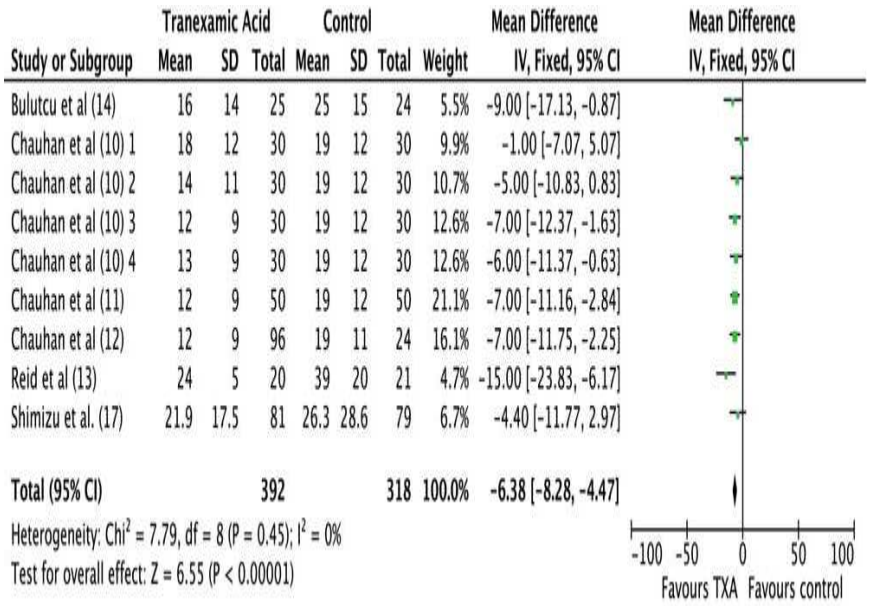


Study or Subgroup	Tranexamic Acid Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Bulutcu et al (14)	34	19	25	40	18	24	7.0%	-6.00 [-16.36, 4.36]
Chauhan et al (10) 1	31	12	30	22	12	30	9.4%	9.00 [2.93, 15.07]
Chauhan et al (10) 2	28	12	30	22	12	30	9.4%	6.00 [-0.07, 12.07]
Chauhan et al (10) 3	20	13	30	22	12	30	9.2%	-2.00 [-8.33, 4.33]
Chauhan et al (10) 4	22	12	30	22	12	30	9.4%	0.00 [-6.07, 6.07]
Chauhan et al (11)	27	14	50	36	18	50	9.2%	-9.00 [-15.32, -2.68]
Chauhan et al (12)	20	9	96	36	12	24	9.9%	-16.00 [-21.13, -10.87]
Levin et al (16)	14.25	8.9	28	17.55	13.2	28	9.5%	-3.30 [-9.20, 2.60]
Reid et al (13)	26	7	20	34	17	21	8.4%	-8.00 [-15.89, -0.11]
Shimizu et al. (17)	18.6	12.8	81	23.5	18.1	79	10.0%	-4.90 [-9.77, -0.03]
Zonis et al (15)	21.1	12	40	27.2	20.3	42	8.8%	-6.10 [-13.28, 1.08]
Total (95% CI)			**460**			**388**	**100.0%**	**-3.61 [-8.08, 0.85]**

Heterogeneity: $Tau^2 = 45.83$; $Chi^2 = 55.11$, df = 10 ($P < 0.00001$); $I^2 = 82\%$

Test for overall effect: $Z = 1.59$ ($P = 0.11$)

* Red cell transfusion



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Chauhan et al (10) 2	14	11	30	19	12	30	10.7%	-5.00 [-10.83, 0.83]
Chauhan et al (10) 3	12	9	30	19	12	30	12.6%	-7.00 [-12.37, -1.63]
Chauhan et al (10) 4	13	9	30	19	12	30	12.6%	-6.00 [-11.37, -0.63]
Chauhan et al (11)	12	9	50	19	12	50	21.1%	-7.00 [-11.16, -2.84]
Chauhan et al (12)	12	9	96	19	11	24	16.1%	-7.00 [-11.75, -2.25]
Reid et al (13)	24	5	20	39	20	21	4.7%	-15.00 [-23.83, -6.17]
Shimizu et al. (17)	21.9	17.5	81	26.3	28.6	79	6.7%	-4.40 [-11.77, 2.97]
Total (95% CI)			**392**			**318**	**100.0%**	**-6.38 [-8.28, -4.47]**

Heterogeneity: $Chi^2 = 7.79$, df = 8 ($P = 0.45$); $I^2 = 0\%$

Test for overall effect: $Z = 6.55$ ($P < 0.00001$)

Faraoni et al Eu J Cardiothorac Surg 2012; 42: 781-786

Tranexamic Acid and Non-Cardiac Surgery

Author	Design	Number	Age	Dose	Effect
Neilipovitz 2001	TXA vs placebo (RCT)	44	8-18	10mg/kg 1mg/kg/hr	Significant reduction in blood loss -250mls (-1123 to 623mls)
Sethna 2005	TXA vs placebo (RCT)	40	9-18	100mg/kg 10mg/kg/hr	Significant reduction in blood loss -855mls (-1408 to -301mls) NS reduction in blood transfusion 0.85 (0.56-1.30
Ng 2016	TXA vs placebo (retrospective cohort)	90 (55/35)	10-23	100mg/kg 10mg/kg/hr	Blood loss decreased by 1.8L vs 3.9L p<0.01, blood transfusion decreased by 77%
Goobie 2011	TXA vs placebo (RCT)	43	2 months – 6 years	50mg/kg 5mg/kg/hr	Significant reduction in blood loss 65mls/kg vs 119mls/kg and blood transfusion 33 vs 56mls/kg
Dadure 2011	TXA vs placebo (RCT)	40	3-15 years	15mg/kg 10mg/kg/hr	Significant reduction in blood loss 7.2mls/kg vs 16.6mls/kg NS reduction in blood transfusion 37% vs 70%

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Target Plasma Levels

In adults:

* in vitro, tranexamic acid inhibits fibrinolysis at a serum concentration of 17.5µg/ml
* Clinically efficacious levels in adults seem to range from 52.5 - 150µg/ml

Wesley MC et al Anesthesiol; 122 (4): 746-758

In children:

* in vitro the plasma level required to inhibit fibrinolysis has been defined as 10µg/ml with suppression of plasmin induced platelet activation at 16µg/ml
* Full inhibition may require concentrations of around 100µl/ml

Grassin-Delyle S et al Anesthesiol 2013; 118 (4); 853-862

In neonates

* in vitro, the plasma level required to inhibit fibrinolysis may be as low as 6.54µg/ml

Yee BE et al Anesth Analg 2013; 117: 767-72

Possible Dosing Regimen for Children undergoing Cardiac Surgery

A Practical Tranexamic Acid Dosing Scheme Based on Population Pharmacokinetics in Children Undergoing Cardiac Surgery

Stanislas Grassin-Delyle, Pharm.D., Ph.D.,* Roland Couturier, M.D.,† Emuri Abe, Pharm.D.,‡ Jean Claude Alvarez, Pharm.D., Ph.D.,§ Philippe Devillier, M.D., Ph.D.,‖ Saïk Urien, M.D., Ph.D.#

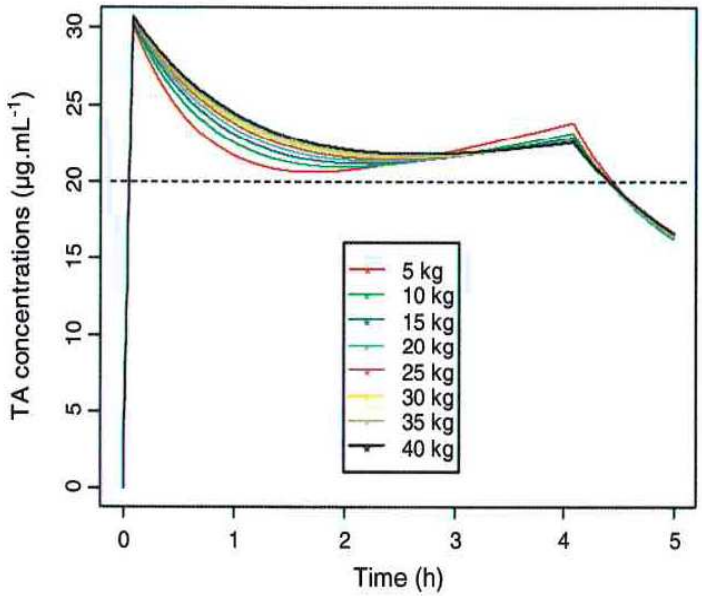

Fig. 5. Dosing simulation to readily obtain a 20-µg/ml tranexamic acid concentration plateau after a 5-min loading dose followed by a 4-h infusion in children with body weights between 5 and 40 kg. The *dotted horizontal line* represents the threshold target concentration of 20 µg/ml. TA = tranexamic acid.

* 21 children mean age 5.35 years randomised to different tranexamic acid regimes
* Serum concentrations measured at 8 time points
* Bolus dose of 6.4mg/kg followed by a weight adjusted infusion of 2.0-3.1mg/kg/hour maintained the concentration between 20 and 30 µg/ml with a low amplitude

Possible Dosing in Neonates and Infants undergoing Cardiac Surgery

Pharmacokinetics of Tranexamic Acid in Neonates, Infants, and Children Undergoing Cardiac Surgery with Cardiopulmonary Bypass

Mark C. Wesley, M.D., Luis M. Pereira, Ph.D., Laurie A. Scharp, B.S., Sitaram M. Emani, M.D., Francis X. McGowan, Jr., M.D., James A. DiNardo, M.D.

* 55 children 2 days – 58 months, 21 sample time points
* Dosing requirements necessary to achieve 20µg/ml in the first year of life change rapidly

	Low
Age	20 µg/ml
0–2 months	
Loading dose (mg/kg)	15
Infusion (mg · kg^{-1} · h^{-1})	2.5
CPB prime dose	20 µg per ml of prime volume
2–12 months	
Loading dose (mg/kg)	9 (6–12)
Infusion (mg · kg^{-1} · h^{-1})	2
CPB prime dose	20 µg per ml of prime volume
>12 months and ≤20 kg	
Loading dose (mg/kg)	4
Infusion (mg · kg^{-1} · h^{-1})	2
CPB prime dose	20 µg per ml of prime volume

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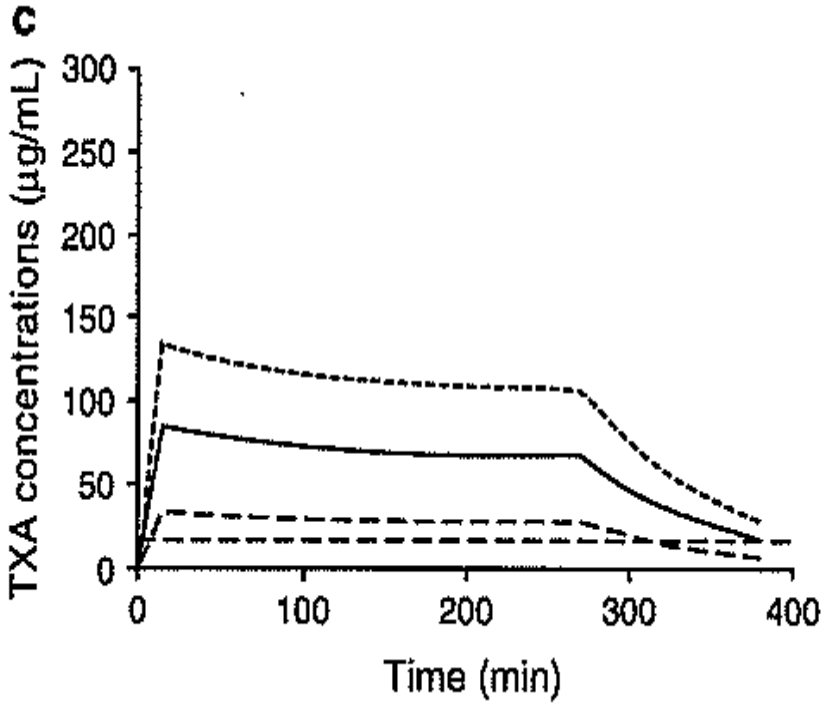
Infusion (mg · kg^{-1} · h^{-1})	2
CPB prime dose	20 µg per ml of prime volume

Possible Dosing Regimen for Children undergoing Non-Cardiac Surgery

Population Pharmacokinetics of Tranexamic Acid in Paediatric Patients Undergoing Craniosynostosis Surgery

Susan M. Goobie · Petra M. Meier · Navil F. Sethna · Sulpicio G. Soriano · David Zurakowski · Snehal Samant · Luis M. Pereira

* 10mg/kg loading dose followed by 5mg/kg/hour to produce a plasma concentration of 16µg/ml



CRASH-2

* randomized placebo-controlled trial
* 20,211 adults in 40 countries
* unstable vitals (systolic blood pressure <90 mmHg and/or heart rate >110 beats per minute, or both) or a high clinical suspicion for significant hemorrhage
* randomized to TXA vs placebo
* significant reduction in risk of death due to bleeding for the TXA group (risk of death 0.85; 95% confidence interval 0.76 to 0.96; *P*?=?0.004, NNT 121
* significant reduction in all-cause mortality (risk of death 0.91; 95% confidence interval 0.85 to 0.97; *P*?=?0.0035, NNT 67

Are children just small adults?

Adults	Children
Trauma tends to be penetrating	Trauma tends to be blunt
Coagulation systems are mature	Coagulation systems may be immature
Vascular structures may be diseased	Vascular structures unlikely to be diseased
the leading cause of mortality is traumatic brain injury, known to be associated with coagulopathy	the leading cause of mortality is traumatic brain injury, known to be associated with coagulopathy
hemorrhage is the second overall cause of death, the first preventable cause of death and first cause of mortality after arrival in hospital.	The incidence of death specifically from hemorrhage with traumatic injuries has not been described in children
25% of adult trauma victims are coagulopathic upon arrival to hospital, ≤ 6% of these have massive hyperfibrinolysis, ≤ 60% have less intense hyperfibrinolysis	27%-77% of the patients may be coagulopathic on arrival to the emergency department, hypofibrinogenemia has been reported in ≤ 52% of children requiring transfusion support

Rationale for the use of tranexamic acid in paediatric trauma

* Trauma is the leading cause of death in children aged 1-18
* Immediate need for transfusion if:
  * Systolic blood pressure low (<80 mmHg <5 years and <90 mmHg ≥5 years)
  * Poor blood pressure response to crystalloid 20–40 ml/kg
  * Obvious significant bleeding

The Hospital for Sick Children Massive Hemorrhage Protocol for the use of tranexamic acid in pediatric trauma. April 2014.

RCPCH

Royal College of
Paediatrics and Child Health

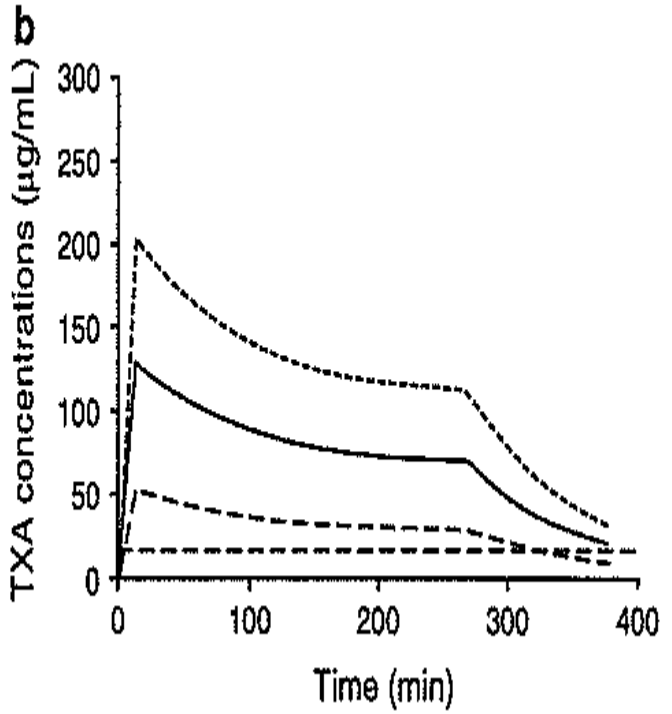
Leading the way in Children's Health

Evidence Statement:
Major trauma and the use of tranexamic acid in children
November 2012

- Tranexamic acid reduces mortality in adult trauma
- Early administration is vital for efficacy
- Due to the lack of published data on the use of tranexamic acid in paediatric patients who have undergone major trauma there is no evidence for a specific dose
- The RCPCH and NPPG Medicines Committee recommend a pragmatic dosage schedule

Suggesting dosing regimen in Paediatric Trauma

Age	Loading Dose	Subsequent Dose
≥12 years: adult protocol	1 g intravenously over 10 minutes and within 3 hours of injury	1 g intravenous infusion over 8 hours
<12 years	15 mg/kg intravenously over 10 minutes (maximum dose 1 g) and within 3 hours of injury	2 mg/kg/hr intravenous infusion over 8 hours or until bleeding stops



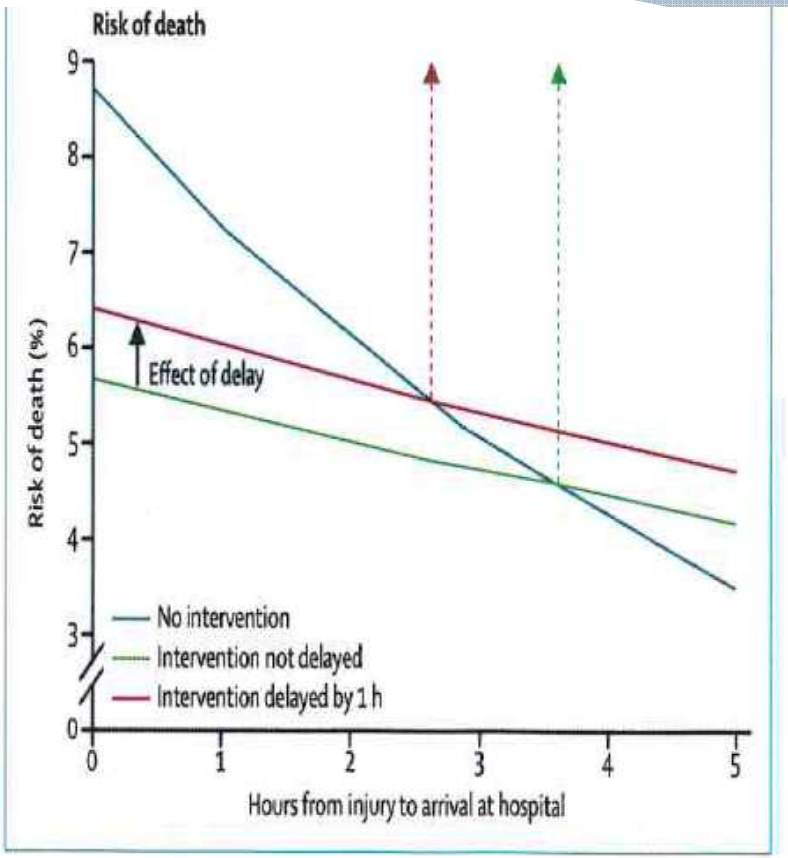
15mg/kg + 5mg/kg/hr

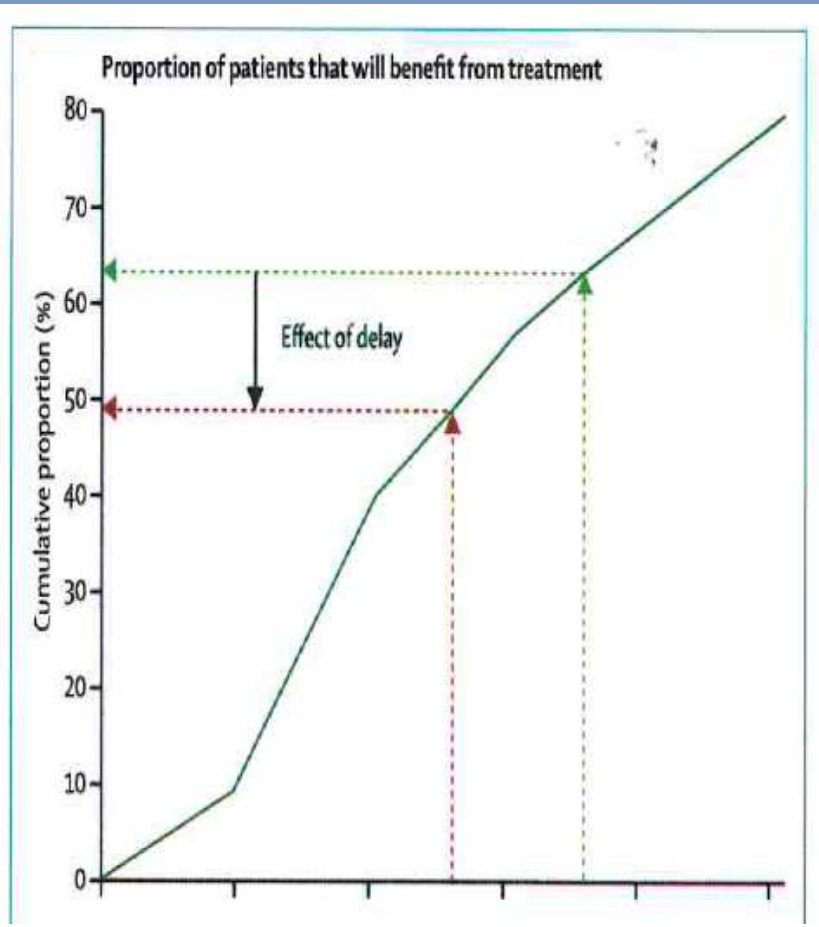
Goobie SM et al Clin Pharmacokinet 2013; 52: 267-276

RCPCH Evidence Statement 2011

The Hospital for Sick Children Massive Hemorrhage Protocol for the use of tranexamic acid in pediatric trauma 2014.

CRASH-2 effect of 1 hour delay in the start of treatment

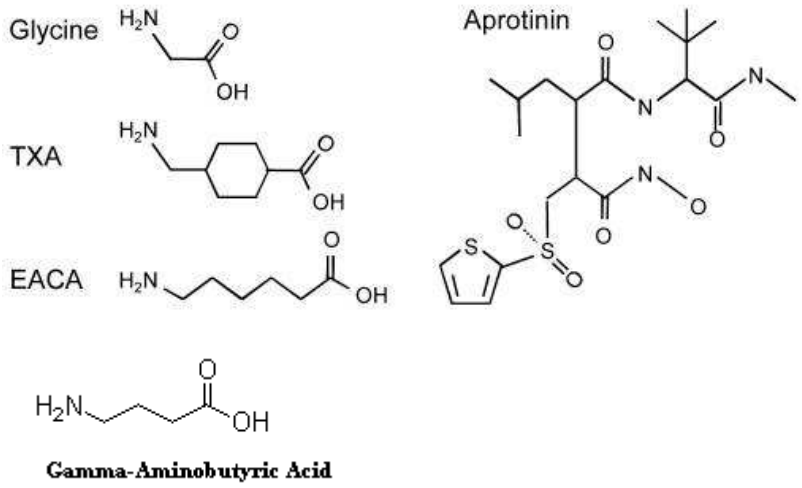




Roberts I et al Lancet 2011; 377: 1071-1072

Side Effects and Cautions

* Seizures - the structural similarity of tranexamic acid to γ-aminobutyric acid (GABA) and glycine; inhibition of these inhibitory receptors by TA results in lowering of the depolarization threshold and enhanced excitability.

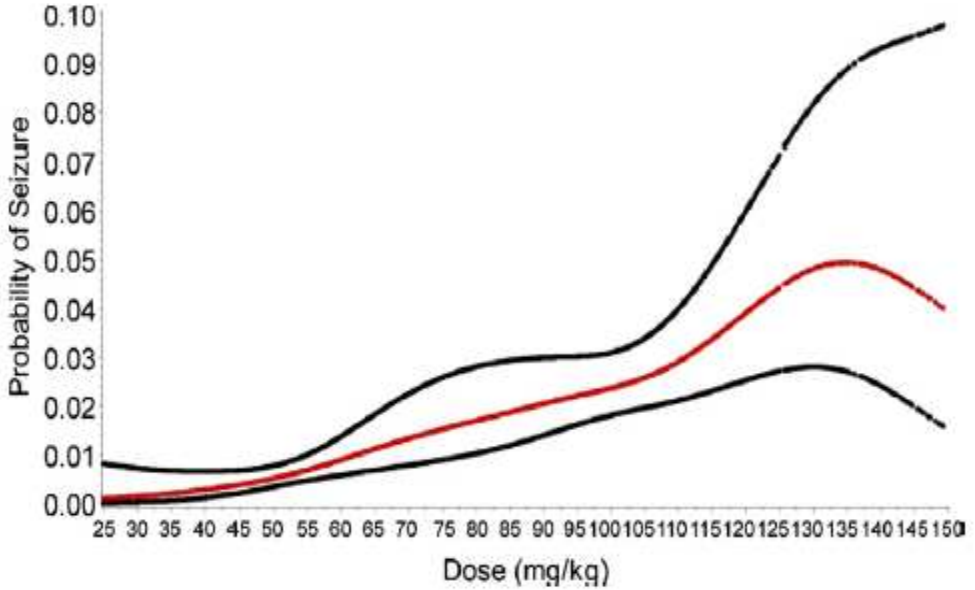


- Thrombosis – there no current evidence that TXA increases the risk of thromboembolic events in children
- DIC
- Massive haematuria
- Significant renal impairment

Tranexamic Acid and Seizures

* Seizures are dose related
* Approximately 95% of tranexamic acid is excreted unchanged in the urine
* excretion decreases with increasing creatinine

Sharma V et al Anaesthesia 2014; 69: 124-130



Risk of early postoperative seizure according to TXA dose with 95% confidence intervals

Kalavrouziotis D et al Ann Thorac Surg 2012; 93:148-55

Conclusions

* Tranexamic acid has been repeatedly shown in multiple small studies to reduce bleeding and transfusion in children, but without an impact on mortality
* Tranexamic acid is shown by cumulative evidence to be a well tolerated drug in children regardless of route of delivery
* Recent pharmacokinetic studies may guide treatment towards ever more appropriate dosing
* Thromboembolism appears no more common than in placebo groups but no studies so far have been adequately powered to look at this
* More research is required to define seizure risk in children

When Should I Use Tranexamic Acid for Children?

* All licenced uses listed in the BNF
* All ages of children undergoing any surgery in which blood loss is likely to be significant i.e. greater than 10% of their circulating volume
* When I am comfortable with the appropriate dose specific to the age/weight of the child and considered the contraindications
* In all ages of children who have suffered significant trauma (and give early!)