

Key points

- 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 in this situation
- The RCPCH and NPPG Medicines Committee recommend a pragmatic dosage schedule – 15mg/kg tranexamic acid loading dose (max 1g) over 10 minutes followed by 2mg/kg per hour

Background information

Major surgery and trauma trigger the body to stimulate a similar haemostatic response, in both of these situations severe blood loss can present a challenge to the coagulation system. Tranexamic acid (TXA) is an antifibrinolytic agent and is used to reduce blood loss in patients during surgery, in order to reduce the risk of post operative complications. The agent acts by blocking the binding sites on plasminogen and can also improve haemostasis by reducing the activation of plasmin-induced platelets.

The CRASH-2 trial showed that administering tranexamic acid within three hours of trauma reduces the risk of death in bleeding adult trauma patients. The data is consistent with the changing practice in adult trauma, but is currently lacking for the use in paediatric trauma patients. This evidence statement is intended to provide guidance on the dose of TXA in major trauma to ensure consistency. It should not preclude the development of suitable robust research studies in this area to improve knowledge.

Efficacy

- The CRASH-2 trial showed that a TXA 1g loading dose over 10 minutes followed by a 1g infusion over 8 hours safely reduced the risk of death in bleeding adult trauma patients.
- In paediatric cardiac surgery, the reported dosing regimens are variable. Significant reductions in total blood loss and total blood or blood product transfusion volume were seen with a variety of dosing regimens.
- TXA doses used to reduce perioperative blood loss and the need for transfusions in scoliosis surgery in children are also variable.
- In surgical corrections of craniosynostosis in children, all regimens showed significant reductions in the need for blood transfusion.
- Short five day courses of oral TXA have been shown to be effective in the treatment of traumatic hyphema in children at a dose of 25mg/kg three times a day.

Safety

- In general, the adverse effects of TXA are rare. They include gastrointestinal effects, malaise with hypotension (on rapid IV injection), arterial or venous thrombosis (see below), dizziness, fatigue, headache, muscle pain and spasms, convulsions, and hypersensitivity reactions including anaphylaxis.
- The use of TXA presents a potential risk of thrombosis. Studies into the use of TXA in paediatric cardiac surgery and spinal surgery did not find any increased rate of thromboembolic events. However, these studies did not have sufficient power to determine safety. An increase in seizure rate may be due to the antagonistic effect of TXA on GABA receptors.

Dosing consensus

A scoping exercise of paediatric centres in the UK revealed a variety of protocols for TXA administration but without a specific evidence base. Following a review of the CRASH 2 trial and available literature in relation to the use of perio-operative TXA in children (submitted for publication) the consensus view of the working group is to recommend a dosing schedule based on the CRASH 2 trial but translated for children. The group agreed that timely administration of TXA preferably within the first 3 hours of trauma for children is likely to be beneficial. In addition a large range of doses up to 100mg/kg have been used in children with very few reported adverse effects.

Dosage:-

Loading Dose – 15mg/kg (max 1g) diluted in a convenient volume of Sodium Chloride 0.9% or Glucose 5% and given over 10 minutes

Maintenance infusion – 2mg/kg/hour. Suggested dilution 500mg in 500ml of sodium chloride 0.9% or glucose 5% given at a rate of 2mls/kg/hour. For at least 8 hours or until bleeding stops.

Practicalities

Intraosseous administration – There is no specific information available about the use of TXA by this route.

This guidance is for children under 12 years of age, for those older than 12 years adult doses should be considered.

A scoping exercise of centres in the UK revealed a variety of protocols. There is no evidence to back up any one in particular. Individual sites may want to review their protocols in light of this recommendation.

Future work

Due to the lack of evidence in this area we recommend that use of TXA in these situations is monitored as closely as possible with data entered as part of the routine datasheet to the Trauma Audit and Research Network (TARN) datasets.

In addition specialised commissioners should consider the need for entry of all children into a suitable research study when commissioning children's trauma services.

Acknowledgments

Mr Andy Fox, Chair, RCPCH/NPPG joint standing Medicines Committee
Dr Ian Maconochie, Clinical Standards Officer, RCPCH
Dr Aung Soe, Clinical Standards, RCPCH consultation co-lead
Dr William van't Hoff, Co-director, Medicines for Children Research Network
Ms Melanie Simpson, Clinical Standards Facilitator, RCPCH
Ms Karina Pall, Research Administrator, RCPCH
RCPCH/NPPG joint Standing Medicines Committee
RCPCH Clinical Standards Committee
Information Support Service to the NPPG at the Welsh Medicines Information Centre
RCPCH Child Health Safety Board

References

- Adams DM, Wentzel MS (2008) The role of the hematologist/oncologist in the care of patients with vascular anomalies. *Pediatr Clin North Am*;55(2):339-55, viii.
- Anderson BJ, Morton G and McKenzie I (2004) The use of antifibrinolytic drugs in paediatric cardiac surgery. *Paediatric and Perinatal Drug Therapy* 6(1)
- Boyle RJ, Nikpour M, Tang ML.(2005) Hereditary angio-oedema in children: a management guideline. *Pediatr Allergy Immunol*;16(4):288-94.
- Chauhan S, Bisoi A, Kumar N, Mittal D, Kale S, Kiran U, Venugopal P (2004) Dose comparison of tranexamic acid in pediatric cardiac surgery. *Asian Cardiovasc Thorac Ann.*;12(2):121-4.
- Chauhan S, Das SN, Bisoi A, Kale S, Kiran U. (2004) Comparison of epsilon aminocaproic acid and tranexamic acid in pediatric cardiac surgery. *J Cardiothorac Vasc Anesth*; 18(2):141-3.
- Dalmau A, Sabaté A, Koo M, Bartolomé C, Rafecas A, Figueras J, Jaurrieta E (2004) The prophylactic use of tranexamic acid and aprotinin in orthotopic liver transplantation: a comparative study. *Liver Transpl*;10(2):279-84.
- Deborah L. Brown, MD (2005) Congenital Bleeding Disorders. *Curr Probl Pediatr Adolesc Health Care*; 35(2):38-62
- Deligeoroglou E, Tsimaris P. (2010) Menstrual disturbances in puberty *Best Pract Res Clin Obstet Gynaecol*;24(2):157-71. Epub
- Eaton MP (2008) Antifibrinolytic therapy in surgery for congenital heart disease. *Anesth Analg*;106(4):1087-100.
- Farkas H, Varga L, Széplaki G, Visy B, Harmat G, Bowen T (2007). Management of hereditary angioedema in pediatric patients. *Pediatrics*.120(3):e713-22.

Hanna M.G, Refaie A., Gouda N., Obaya G. (2010) Reduction of peri-operative bleeding in craniofacial surgeries in pediatrics. Comparison between recombinant factor VII and tranexamic acid. *Egyptian Journal of Anaesthesia*. 26(1): 53-61.

Information Support Service to the NPPG at the Welsh Medicines Information Centre (2012) Review of the use of tranexamic acid in children.

Mathew P, Young G. (2006) Relationship between factor VII activity and clinical efficacy of recombinant factor VIIa given by continuous infusion to patients with factor VIII inhibitors. *Recombinant factor VIIa in paediatric bleeding disorders--a 2006 review*. *Haemophilia*;12(5):457-72.

Neilipovitz DT, Murto K, Hall L, Barrowman NJ, Splinter WM (2001) A randomized trial of tranexamic acid to reduce blood transfusion for scoliosis surgery *Anesth Analg*;93(1):82-7.

Powell RJ, Du Toit GL, Siddique N, Leech SC, Dixon TA, Clark AT, Mirakian R, Walker SM, Huber PA, Nasser SM (2007) BSACI guidelines for the management of chronic urticaria and angio-oedema. *Clin Exp Allergy*;37(5):631-50.

Price VE, Hawes SA, Chan AK. (2007) A practical approach to hemophilia care in children *Paediatr Child Health*; 2(5):381-3.

Roberts I et al CRASH -2 collaborators (2011) The importance of early treatment with tranexamic acid in bleeding trauma patients: an exploratory analysis of the CRASH-2 randomised controlled trial. *Lancet*; DOI:10.1016/S0140-6736(11)60278-X

Rodriguez NI, Hoots WK (2008) Advances in hemophilia: experimental aspects and therapy. *Pediatr Clin North Am*;55(2):357-76, viii.

Santagostino E, Morfini M, Rocino A, Baudo F, Scaraggi FA, Gringeri A (2001) *Thromb Haemost*;86(4):954-8.

Tzortzopoulou A, Cepeda MS, Schumann R, Carr DB (2008) Antifibrinolytic agents for reducing blood loss in scoliosis surgery in children. *Cochrane Database Syst Rev*; 16;(3):CD006883

Vacharaksa K, Prakanrattana U, Suksompong S, Chumpathong S (2002) Tranexamic acid as a means of reducing the need for blood and blood component therapy in children undergoing open heart surgery for congenital cyanotic heart disease. *J Med Assoc Thai*;85 Suppl 3:S904-9

Zonis Z, Seear M, Reichert C, Sett S, Allen C (1996) The effect of preoperative tranexamic acid on blood loss after cardiac operations in children. *Journal of Thoracic Cardiovascular Surgery*;111(5):982-7.