

Tranexamic acid for fractured neck of femur?

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What is Tranexamic Acid?

- Tranexamic Acid (TA) was first discovered in 1964 in Japan and has been widely available for use for over 20 years.
- It is an anti fibrinolytic preventing the breakdown of fibrin clot into fibrin degradation products
- The clinical concern has always been that by effectively promoting clot stability this will mean that an increase in the incidence of DVT, PE, MI and CVE will be seen.



Clot Breakdown (fibrinolysis)

Fibrin+ plasminogen in clot





Fibrinolysis with plasmin breaking fibrin down to fibrin degradation products

How does TXA inhibit fibrinolysis?





Inhibition of fibrinolysis



CRASH-2 trial 2010



- 20 000 patients treated within 8 hours of injury to either 2g TA (1g load and then 1 g over 8 hours iv) or placebo
- All cause mortality was 14.5% in the TXA group and 16% in the placebo group
- Bleeding related mortality was reduced (4.9% vs 5.7%)
- There was no increase in fatal or non fatal vascular occlusive events.

Caveats to CRASH-2 safety data.....

- Although we recorded no increased risk of nonfatal, vascular occlusive events with tranexamic acid, the precision of the estimates was low and we cannot exclude the possibility of some increase in risk.'
- 'we sought high specificity in the diagnosis of nonfatal vascular occlusive events and stipulated that occlusive events should be recorded only when there was clear clinical evidence. As a result, we might have under-reported the frequency of these events.'
- Average age of patient in CRASH-2 was 32yrs



Cochrane Review 2011: Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion.



- 252 Studies, 25 000 patients
- 30% reduction in need for transfusion
- No increase in MI, stroke or mortality but data described as 'sparse'
- There are concerns about the adequacy of reporting of uncommon events in the small clinical trials included in this review

Effect of tranexamic acid on surgical bleeding: systematic review and cumulative meta-analysis BMJ 2012 –Ker et al British Medical Journal

- 129 trials over 10 000 patients
- Reduced need for transfusion by 30% 'strong evidence that tranexamic acid reduces transfusion in surgery has been available for many years'
- 'The evidence that tranexamic acid reduces the need for blood transfusion is strong but the safety of routine use of tranexamic acid in surgical patients remains uncertain. A modest increase in the risk of thromboembolic effects could outweigh the benefits of reduced blood use.'
- Surgical patients should be made aware of this evidence so that they can make an informed choice.'

The evidence used by NICE for Tranexamic Acid



National Institute for Health and Clinical Excellence

- Moderate blood loss: 52 papers, 43 in elective THR or TKR
 - 2 In hip fracture
 - 2 in maxilo facial surgery
 - 2 spinal surgery
 - 1 CABG
 - I myomectomy
 - 1 radical prostatectomy
- High Blood Loss: 45 papers, 40 in cardio/thoracic surgery
 - 2 liver surgery
 - 1 major orthopaedic surgery
 - 1 ovarian cancer surgery
 - 1 spinal surgery

So what can we conclude?

- There is very good evidence that tranexamic acid reduces the need for blood transfusion in surgical patients by 30%
- In patients at high risk of bleeding over 1000mls there is evidence for improved mortality
- It has been safely and widely used for many years in surgical patients, some at high risk of thrombosis. Assuming effective thromboprophylaxis measures there is no emerging evidence of excessive thrombosis, the odd case report is all there is at the moment
- It is cheap and therefore cost effective to use



So what can we conclude?



- There are very few studies, perhaps only CRASH-2 so far powered to identify increases in pulmonary embolus
- Particularly in the developed world where transfusion is now so safe, a 'modest increase in the risk of thromboembolic events could outweigh the benefits of reduced blood loss' Ker BMJ 2012
- The evidence especially in elective surgery is from a small number of specialities namely cardiac and orthopaedic surgery

What are we doing in RD&E?



- Obstetricians have decided to wait until WOMAN study
- Vascular surgeons using for their larger vessel ops, still concern for small vessel disease such as amputation where blood loss not that much anyway
- Colorectal surgeons wary because of lack of evidence from cancer patients
- Not being used routinely in fractured neck of femur



Spot the difference.....

- Hip Fracture patient
 - Average length of stay 12 days
 - Older, frailer and not on the telly....



- Elective Hip Arthroplasty patient
 - Average length of stay 3 days
 - Younger fitter and on the telly....





Systematic Review of the use of Tranexamic Acid in hip fracture patients. Charity 2016



- 6 Randomised controlled double blind studies with 200 active patients and 200 control patients
- Patients receiving TXA per operatively were significantly less likely to receive transfused blood (RRR 0.59)
- There was insufficient data to conclude whether there was an increase in vascular events

A systematic review of Tranexamic acid in hip fracture surgery, Farrow et al 2016



- 341 patients received TXA, 429 Controls
- Found an absolute risk reduction of 12 % in number of people transfused, NNT of 8
- Mean post op haemoglobin significantly higher in patients given TXA (9g/l)
- 'understanding the thrombotic risk associated with TXA use in hip fracture surgery is of paramount importance to determining its clinical utility'
- 'Only large studies are likely to provide sufficient cohort size to accurately determine thrombosis risk'

Audit of blood use in hip fracture patients RD&E 2014



- 613 Patients had hip fracture surgery in 2014
- 190 Transfused, 31%
- Average number of units 2.2 per patient transfused
- 418 units of blood used in hip fracture, about 5% of our total blood use in RD&E

HipFrac TXA Study

- Proposal for a large RCT double blind multicentre study run by the University of Exeter Medical School
- 8800 patients needed, recruit from 80 hospitals, powered to detect increase in mortality and risk of thrombosis
 - Primary outcome measure is 30 day mortality
 - Secondary Outcomes
 - Risk of thrombosis within 120 days surgery
 - Number of patients requiring transfusion
 - Post operative haemoglobin
 - Length of hospital stay
 - Quality of life and mobility



Conclusions



- Tranexamic acid significantly reduces the need for transfusion across a wide range of surgical operations, including hip fracture surgery
- Blood transfusion very safe in UK, so a modest increase in the risk of thromboembolic effects could outweigh the benefits of reduced blood use.
- NICE and AAGBI 2015/16 give to all where blood loss expected to be 500 mls or more
- Pragmatists vs Purists: Do we need a trial???