Institution: University of Leicester

Unit of Assessment: UoA1 Clinical Medicine

Title of case study: A new use for an old drug: administration of tranexamic acid to prevent trauma deaths from bleeding

1. Summary of the impact

Trauma is a rapidly increasing global healthcare problem which is predicted by the World Health Organisation (WHO) to overtake infectious disease globally by 2020. The discovery of the acute coagulopathy of trauma (uncontrolled bleeding) and the subsequent establishment of the clot stabiliser tranexamic acid (TXA) as a treatment for this condition has led to a change in national and international trauma management protocols. British armed forces and the US military implemented the use of the drug soon after the results were published. Every injured British or American soldier now receives this treatment. The use of TXA has been included in national and international guidance for trauma care.

2. Underpinning research

Background

Prior to Professor Tim Coats' appointment to the University of Leicester as Professor of Emergency Medicine in 2004, he had published the first description of the acute coagulopathy of trauma (uncontrolled bleeding). Coats had the idea that an antifibrinolytic (a drug that prevents clots from breaking down) might be a potential treatment for this newly discovered condition. The original CRASH trial (of steroids in head injury – no University of Leicester involvement) had just finished, so upon joining Leicester Coats had discussions with Professor Ian Roberts of the London School of Hygiene and Tropical Medicine (LSHTM) to see if the same set of research sites could be used for an antifibrinolytic trial in major trauma. The drug was tranexamic acid (TXA), a cheap-to-produce and widely available treatment that had been used for some time in operating theatres to prevent the need for blood transfusions. In 2004 Coats published a Cochrane Review (**1**) of the evidence for the use of TXA in trauma, which demonstrated that the existing evidence was very poor and that a large clinical trial was needed to answer the question.

CRASH2 trial

In 2005 a large randomised trial, called CRASH2, of tranexamic acid treatment in patients who had or were suspected to have significant bleeding was initiated. Coats, who had originated the idea and developed the methodology, was the clinical lead and Leicester was the lead clinical centre for the UK. Roberts was the Lead Applicant and Chief Investigator for the worldwide CRASH2 trial (20,000 patients in 274 hospitals in 40 countries) and LSHTM's clinical trials unit, with its large-scale delivery system, ran the trial, assisted by a worldwide group of trauma clinicians.

The unit was responsible for input into the design of a practical pragmatic trial that could be delivered in emergency care, the estimate of the likely mortality for the sample size calculation, the engagement of emergency physicians, and the practicalities of trial delivery in the new regulatory framework. Coats was a member of the Trial Management Group, the Trial Steering Group and the Writing Committee.

One life saved for every 67 patients treated

The trial showed that treatment with tranexamic acid reduced patient mortality from 16% (control group) to 14.5% (TXA group), thus preventing 9% of all trauma deaths – in other words one life was saved for every 67 patients treated. The reduction in the relative risk of death due to bleeding was even higher, at 15%. There was no increase in adverse events such as thrombosis. The economic analysis estimated that approximately 100,000 lives per year worldwide (15% of in-hospital trauma deaths from bleeding) could be saved by widespread use of the results of this research.

The trial results were published in The Lancet in 2010 (**2**) and a subsequent subgroup analysis (on time from injury to administration) was published as a separate paper in The Lancet in 2011 (**3**). An analysis of the specific effects in bleeding patients was published in the BMJ in 2012 (**4**). The original 2004 Cochrane Review (for which Coats was first author) was updated in 2012 (**5**; Coats became last author).

3. References to the research

1. Antifibrinolytic drugs for acute traumatic injury. Coats TJ, Roberts I, Shakur H, Cochrane Database Syst Rev. 2004; 4.

2. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. CRASH-2 trial collaborators. The Lancet. 2010; 376(9734):23-32.doi:10.1016/S0140-6736(10)60835-5

3. The importance of early treatment with tranexamic acid in bleeding trauma patients: an exploratory analysis of the CRASH-2 randomised controlled trial. CRASH-2 collaborators. The Lancet 2011; 377: 1096 – 1101. doi:10.1016/S0140-6736(11)60278-X

4. Effect of tranexamic acid on mortality in patients with traumatic bleeding: pre-specified analysis of data from a randomised controlled trial. Roberts I, Perel P, Prieto-Merino, Shakur H, Coats T, Hunt B, Lecky F, Brohi K, Willett K, CRASH-2 Collaborators BMJ. 2012 Sep 11;345. http://www.bmj.com/content/345/bmj.e5839

5. Antifibrinolytic drugs for acute traumatic injury. Roberts I, Shakur H, Ker K, Coats T; CRASH-2 Trial collaborators. Cochrane Database Syst Rev. 2012;12: CD004896. doi: 10.1002/14651858.CD004896.pub3

Grants
BUPA Foundation (2005) £220, 000
Molton Foundation (2005) £196, 000
NIHR HTA (2007) £2.8 million (Coats was a co-applicant)

4. Details of the impact

The outcome of the CRASH2 trial has been a worldwide change in protocols and practice, with treatment using TXA now being regarded as the standard of care in severe injury.

Once fully implemented, TXA could prevent 15% of in-hospital deaths from bleeding following trauma each year (around 100,000 per year), giving a worldwide health cost-benefit of £26 billion per year (assuming £20,000 per Quality Adjusted Life Year). Around 600 lives could be saved in Britain each year. A single dose of TXA costs around £3, so there are no substantial cost implications to its widespread adoption.

Impact on the battlefield
As uncontrolled bleeding is the leading cause of preventable death among combat casualties, it was not surprising that within weeks the British armed forces and US military were working with the CRASH2 team to implement the use of TXA on the battlefield. British armed forces protocols were changed in 20101 (**A**) and the US military Standard Operation Procedures changed in 2012 (**B**).

A 2011 registry-based study of combat injured troops receiving blood at the Bastion Role 3 facility in Afghanistan has demonstrated findings supportive of TXA use: the group receiving TXA had a lower mortality rate (17.4%) than the no-TXA group (23.9%) despite being more severely injured.

In 2012 the drug box onboard the US presidential plane 'Air Force One' was updated to include TXA (supporting evidence not available as classified).

Impact on civilian practice in the UK
The rotation of Territorial Army / Home Guard trauma clinicians through combat deployments greatly aided in spreading the implementation of the results into civilian practice. In the UK, the research has changed patient care, being incorporated into both national and local trauma care guidelines across the UK (**C,D**).

The Joint Royal Colleges Ambulance Liaison Committee has changed ambulance protocols (2013) to mandate that all severely injured patients in the UK are given TXA in the prehospital phase of trauma care (**E**).

The National Institute for Health and Care Excellence (NICE) was initially unable to comment on the research as its constitution does not allow it to comment on 'off label' indications; however, after some discussion a new category of NICE activity has been developed and the research has resulted in the first NICE Evidence Summary of Unlicensed/off-label Medicine (**F**).

Within the wider NHS the results of the research have been chosen as one of the key components of the 2013/14 'Payment by Results' system for trauma care, with the supporting documentation specifically mentioning the high quality of the evidence (**G**).

International impact
The standard European Guideline for the management of bleeding after trauma (for which Prof. Coats is a co-author) was modified in 2013 to include the results of this research as a Grade 1A recommendation (there are only four recommendations of this grade in the guidelines; **H**).

In 2012 the CRASH2 team successfully applied to the WHO 'Essential Medicines' Committee for tranexamic acid to be included in the WHO List of Essential Medicines, which guarantees availability of tranexamic acid in the developing world (**I**). This is a very important step towards maximising the impact of this research, as trauma is a disease epidemic in the developing world: 90% of trauma deaths are in low and middle-income countries, and the potential of TXA to reduce premature mortality is likely to be much greater in these settings. Of the 100,000 lives that could potentially be saved each year, around a quarter are in India and China (**J**). TXA is cheap to produce, widely available and easy to administer, making it ideal for use in low and middle-income countries where healthcare budgets may be limited.

Sources to corroborate the impact

A. British Forces News: Injured soldiers in Afghanistan saved by blood-clotting drug (19 January 2011). http://www.youtube.com/watch?v=oj6P2cwwRYw

B. Tranexamic Acid (TXA) in Tactical Combat Casualty Care Guideline Revision Recommendation Committee on Tactical Combat Casualty Care. 11 August 2011. http://www.medicalsci.com/files/tranexamic_acid__txa__in_tactical_combat_casualty_care.pdf

C. Peninsula CLAHRC Tranexamic Acid Guideline. http://www.clahrc-peninsula.nihr.ac.uk/includes/site/files/files/CRASH%202/SW%20Hospital%20TXA%20guideline%20final.pdf

D. RCPCH Evidence Statement - Major trauma and the use of tranexamic acid in children. Royal College of Paediatrics and Child Health. November 2012. https://www.tarn.ac.uk/content/downloads/3100/121112_TXA%20evidence%20statement_final%20v2.pdf

E. Joint Royal Colleges Ambulance Liaison Committee. Guidelines 2012 - Trauma. (no electronic copy available as a restricted document).

F. ESUOM1 Significant haemorrhage following trauma: tranexamic acid. National Institute for

Health and Care Excellence. October 2012.
http://www.nice.org.uk/mpc/evidencesummariesunlicensedofflabelmedicines/ESUOM1.jsp

G. Payment by Result Guidance for 2013-14. Department of Health 2013.
https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/127296/Draft-PbR-Guidance-for-2013-14-not-accessible.pdf.pdf (Paragraph 424)

H. Management of bleeding and coagulopathy following major trauma: an updated European guideline. Spahn DR, Bouillon B, Cerny V, Coats TJ, Duranteau J, Enrique Fernández-Mondéjar E, Filipescu D, Hunt BJ, Komadina R, Nardi G, Neugebauer E, Ozier Y, Riddez L, Schultz A, Vincent JL and Rossaint R Critical Care 2013, 17:R76 http://ccforum.com/content/17/2/R76/ (Recommendation 24)

I. WHO 18th Expert Committee on the Selection and Use of Essential Medicines
Proposal for the inclusion of Tranexamic Acid (anti-fibrinolytic - lysine analogue) in the WHO Model List of Essential Medicines. World Health Organisation 2011.
http://www.who.int/selection_medicines/committees/expert/18/applications/TRANEXAMIC_ACID_10_2.pdf

J. Ker K, Kiriya J, Perel P, Edwards P, Shakur H, Roberts I. Avoidable mortality from giving tranexamic acid to bleeding trauma patients: an estimation based on WHO mortality data, a systematic literature review and data from the CRASH-2 trial. BMC Emerg Med 2012; 12: 3.