What’s good and bad in resuscitation: CRASH vs CONTROL

Michael Parr
Liverpool Hospital
UNSW
Sydney, Australia
Antifibrinolytic drugs for acute traumatic injury (Review)

Coats T, Roberts IG, Shakur H

- Antifibrinolytic treatment reduces blood loss following surgery…may be effective in trauma

- Aprotinin, tranexamic acid, epsilon-aminocaproic acid

- Conclusion: Inadequate data to make a recommendation
Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage

A large randomised placebo controlled trial among trauma patients with, or at risk of, significant haemorrhage, of the effects of antifibrinolytic treatment on death and transfusion requirement.

INTRANET FOR COLLABORATORS

The CRASH-2 trial is scheduled to end by the end of 2009. Therefore we are not looking to recruit any new hospitals to participate. If you would like to receive the trial results when they are published in 2010, you can register your interest here.

Peer reviewed Protocol is available on The Lancet protocol website »»» CLICK HERE

17,537 patients randomised
Last updated Fri 04-Sep-2009 17:08 BST

118 days to go!
2,463 patients to recruit

*** CONGRATULATIONS TO DANIEL KINYURO OJUKA & TEAM IN KAPEN!***
Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage

A large randomised placebo controlled trial among trauma patients with, or at risk of, significant haemorrhage, of the effects of antifibrinolytic treatment on death and transfusion requirement

20,000 PATIENTS RANDOMISED

Congratulations to all our 274 collaborating hospitals in 40 countries for completing the randomisation of 20,000 patients!

FINAL RESULTS PUBLISHED ON LANCET ONLINE ON 15 JUNE 2010

pdf-version

Abstract in Spanish - Hindi - Chinese - Japanese

PUBLISHED ON LANCET ONLINE 24 MARCH 2011

CRASH-2 subgroup analysis: 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
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*
• 274 hospitals in 40 countries
• 20,211 adult trauma patients “with, or at risk of, significant bleeding”
• within 8 h of injury
• either tranexamic acid (loading dose 1 g over 10 min then infusion of 1 g over 8 h) or placebo.
• Double blinded

• The primary outcome = death in hospital within 4 weeks of injury, described by categories: bleeding, vascular occlusion (myocardial infarction, stroke and pulmonary embolism), multiorgan failure, head injury, and other. All analyses were by intention to treat.
**PATIENT ENTRY FORM**

**CRASH2 PATIENT ENTRY INTERNATIONAL**

**INFORMATION ABOUT YOUR HOSPITAL**

1. Country
2. Name of hospital (or your hospital code)
3. Name of caller

**INFORMATION ABOUT THE PATIENT**

4. Patient sex (please circle)  |  Male | Female
5. Patient initials
6. Patient hospital identification number
7. Do you know patient’s date of birth?
   a. YES – date of birth
   b. NO – approximate age

**INFORMATION ABOUT THE INJURY**

8. Estimated number of hours since injury
9. Type of injury (please circle)  | 1 Blunt  | 2 Penetrating  | 3 Both

**FIRST MEASUREMENT IN HOSPITAL OF THE FOLLOWING (IF UNKNOWN GIVE VALUE AT RANDOMISATION)**

10. Systolic BP (mmHg)
11. Respiratory rate (per min)
12. Central capillary refill time (sec)
13. Heart rate (per min)
14. Glasgow Coma Score (max 15)

**Now call Randomisation Service with these answers and write down the treatment pack number given at the end of the phone call**

**Box □ □ □ □ Pack □ □**

Get this pack and follow the instructions on it carefully

Or paper randomise as per instructions in site file
### CRASH2 OUTCOME FORM

**1. HOSPITAL**
- Patient Initials
- Hospital ID Number
- Sex (M/F)
- Date of Birth

**2. PATIENT**
- Patient Details
- Patient ID
- Sex (M/F)
- Date of Birth
- Box and treatment pack number allocated at entry
- Date randomised

**3. OUTCOME**
- 3.1 DEATH IN HOSPITAL
  - Date of death
  - Cause of death: Bleeding, Head Injury, Myocardial Infarction, Stroke, Pulmonary Embolism, Multi organ failure, Other
- 3.2 PATIENT ALIVE
  - Discharged: Date of discharge
  - Still in this hospital now: Date
  - No symptoms
  - Minor symptoms
  - Some restriction in lifestyle but independent
  - Dependent, but not requiring constant attention
  - Fully dependent, requiring attention day and night

**4. MANAGEMENT**
- Days in Intensive Care Unit
- Significant Head Injury
- Neurosurgical
- Chest
- Abdomen
- Pelvis

**5. COMPLICATIONS**
- Pulmonary Embolism
- Deep Vein Thrombosis
- Stroke
- Operation for bleeding
- Myocardial Infarction
- Gastrointestinal bleeding

**6. TRIAL TREATMENT**
- Complete loading dose given
- Complete maintenance dose given

**7. TRANSFUSION**
- Blood products transfusion
- Units transfused in 28 days
- Red cell products
- Fresh frozen plasma
- Platelets
- Cryoprecipitate
- Recombinant Factor VIII

**8. PERSON COMPLETING FORM**
- Name
- Position

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### CRASH2 SERIOUS ADVERSE EVENT REPORT

**1. NAME OF RESPONSIBLE CLINICIAN (PLEASE PRINT):**
- Name
- Position
- Telephone

**2. PATIENT DETAILS**
- Patient Initials
- Patient ID
- Sex (M/F)
- Date of Birth
- Box and treatment pack number allocated at entry
- Date randomised

**3. OUTCOME**
- Resulted
- Life-threatening
- Prolongation of hospitalisation
- Persistent or significant disability
- Other (not covered by categories above, in the investigator's opinion, should be considered serious)

**4. ADVERSE EVENT DETAILS**
- Date of onset
- Time of onset (24hr clock)
- End date

Please describe the adverse event:

Please state why you suspect the adverse event to be related to the study drug:

How likely do you think this event was trial drug related? (0 - 100%) %

Signature
- Date

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**Version 1**
- Date 15/10/04
- Protocol Code: ISRCTN96750102
20,211 randomised

10,096 allocated to tranexamic acid
  3 consent withdrawn
  10,093 had baseline data
    9,995 received allocated loading dose
    9,490 received allocated maintenance dose
    33 no follow-up
  10,060 analysed

10,115 allocated to placebo
  1 consent withdrawn
  10,114 had baseline data
    9,989 received allocated loading dose
    9,475 received allocated maintenance dose
    47 no follow-up
  10,067 analysed
Results

- All-cause mortality was significantly reduced with tranexamic acid (1463 [14.5%] tranexamic acid group vs 1613 [16.0%] placebo group; relative risk 0.91, 95% CI 0.85–0.97; p=0.0035).

- The risk of death due to bleeding was significantly reduced (489 [4.9%] vs 574 [5.7%]; relative risk 0.85, 95% CI 0.76–0.96; p=0.0077).

- Interpretation Tranexamic acid safely reduced the risk of death in bleeding trauma patients in this study. On the basis of these results, tranexamic acid should be considered for use in bleeding trauma patients.
1. Do you have numbers that were excluded from study because the responsible Dr thought tranexamic acid was definitely indicated or contraindicated?

We do not have numbers but in practice the uncertainty principle was largely a theoretical issue given the lack of any prior evidence.

2. Were any patients excluded on the basis of futility i.e. expected to die?

Again we don't know but in general it makes no sense to give any trial treatment to a patient certain to die.

3. Why do you think the mortality was only 15% versus your powered estimate of 20%?

Sample size calculations are always a guess and being 5% off is within the margin of error.
MP 4. Were patients who died of 'bleeding' equally likely to receive/not receive blood products?

IR Haven’t done this analysis but the problem of competing risks always needs to be taken into account. In other words, where there is a 15% reduction in bleeding mortality it becomes very difficult to interpret the blood transfusion data. Because there are substantially fewer deaths in the TXA treated group - there are more patients alive who have the opportunity to receive a blood transfusion. We have done sensitivity analysis assuming that the patients who died in the placebo group as a result of not receiving TXA- had not died and received a blood transfusion - in this case there would be a significant reduction in transfusion.

MP 5. Why do you think the result is the opposite of elective surgical studies that show reduced blood product use but no difference in mortality?

IR Again - competing risks is a big problem. Plus the reasons that we give in the paper.

MP 6. Do you have info to calculate Median ISS?

IR No we don't.
### Table 1

<table>
<thead>
<tr>
<th>REGION</th>
<th>RR</th>
<th>99% Conf. Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asia</td>
<td>0.92</td>
<td>0.80 – 1.05</td>
</tr>
<tr>
<td>Central and South America</td>
<td>0.90</td>
<td>0.76 – 1.06</td>
</tr>
<tr>
<td>Africa</td>
<td>0.90</td>
<td>0.75 – 1.08</td>
</tr>
<tr>
<td>North America, Europe, Australia</td>
<td>0.90</td>
<td>0.70 – 1.15</td>
</tr>
</tbody>
</table>

Table 1 shows the effect of TXA on mortality by geographic region. There was no significant difference in the effect of TXA by region.

### Table 2

<table>
<thead>
<tr>
<th>GENDER</th>
<th>RR</th>
<th>99% Conf. Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>0.92</td>
<td>0.84 – 1.00</td>
</tr>
<tr>
<td>Female</td>
<td>0.86</td>
<td>0.70 – 1.06</td>
</tr>
</tbody>
</table>

Table 2 shows the effect of TXA on mortality by sex. There was no significant difference in the effect of TXA by sex.
Bleeding deaths: geographical region

<table>
<thead>
<tr>
<th>Region</th>
<th>Hospitals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Region 1</td>
<td>114</td>
</tr>
<tr>
<td>Region 2</td>
<td>56</td>
</tr>
<tr>
<td>Region 3</td>
<td>52</td>
</tr>
<tr>
<td>Region 4</td>
<td>48</td>
</tr>
<tr>
<td>World</td>
<td></td>
</tr>
</tbody>
</table>

RR (95% CI)

\[ \text{chi}^2 = 1.445 \quad \text{Pr} \cdot \text{chi}^2 = 0.6950 \]
The importance of early treatment with tranexamic acid in bleeding trauma patients: an exploratory analysis of the CRASH-2 randomised controlled trial

The CRASH-2 collaborators*
• Because tranexamic acid is thought to exert its effect through inhibition of fibrinolysis, we undertook exploratory analyses of its effect on death due to bleeding.

• We examined the effect of tranexamic acid on death due to bleeding according to time to treatment, severity of haemorrhage as assessed by systolic blood pressure, Glasgow coma score (GCS), and type of injury. All analyses were by intention to treat.
Results:

- Early treatment (≤1 h from injury) significantly reduced the risk of death due to bleeding (198/3747 [5.3%] events in tranexamic acid group vs 286/3704 [7.7%] in placebo group; relative risk [RR] 0.68, 95% CI 0.57–0.82; p<0.0001).
- Treatment given between 1 and 3 h also reduced the risk of death due to bleeding (147/3037 [4.8%] vs 184/2996 [6.1%]; RR 0.79, 0.64–0.97; p=0.03).
- Treatment given after 3 h seemed to increase the risk of death due to bleeding (144/3272 [4.4%] vs 103/3362 [3.1%]; RR 1.44, 1.12–1.84; p=0.004).
- We recorded no evidence that the effect of tranexamic acid on death due to bleeding varied by systolic blood pressure, Glasgow coma score, or type of injury.
Interpretation

- Tranexamic acid should be given as early as possible to bleeding trauma patients. For trauma patients admitted late after injury, tranexamic acid is less effective and could be harmful.
Cost-Effectiveness Analysis of Administering Tranexamic Acid to Bleeding Trauma Patients Using Evidence from the CRASH-2 Trial

Carla Guerriero¹*, John Cairns¹, Pablo Perel², Haleema Shakur², Ian Roberts², on behalf of CRASH 2 trial collaborators

• TXA within 3 hours of injury saved an estimated 372, 315 and 755 LYs per 1,000 trauma patients in Tanzania, India and the UK respectively.

• Cost of TXA/1,000 patients=$17,483 Tanzania, $19,550 India and $30,830 in the UK.

• Incremental cost per LY gained of administering TXA is $48, $66 and $64 in Tanzania, India and the UK respectively.

• Early administration of TXA to bleeding trauma patients is likely to be highly cost effective in low, middle and high income settings.
Michael Parr was Chairman of an Australian NovoNordisk Advisory Board, member of a NovoNordisk International Trauma Education Advisory Board, and member of the CONTROL trial steering committee.
First Case Report

Treatment of traumatic bleeding with recombinant factor VIIa

Gili Kenet, Raphael Walden, Arieh Eldad, Uri Martinowitz

Surgical intervention failed to stop life-threatening bleeding caused by injury complicated by severe coagulopathy. Administration of recombinant factor VIIa immediately corrected the coagulopathy and bleeding stopped.

THE LANCET • Vol 354 • November 27, 1999
Recombinant Factor VIIa as Adjunctive Therapy for Bleeding Control in Severely Injured Trauma Patients: Two Parallel Randomized, Placebo-Controlled, Double-Blind Clinical Trials

Kenneth David Boffard, MD, Bruno Riou, MD, PhD, Brian Warren, MD, Philip Iau Tsau Choong, MD, Sandro Rizoli, MD, Rolf Rossaint, MD, Mads Axelsen, MD, and Yoram Kluger, MD, for the NovoSeven Trauma Study Group

• Conclusion:
  rFVIIa resulted in a significant reduction in RBC transfusion in severe blunt trauma.
  The safety of rFVIIa was established in these trauma populations within the investigated dose range.

  J Trauma. 2005;59:8 –18.
Phase III study

A multi-center, randomized, double-blind, parallel group, placebo controlled trial to evaluate the efficacy and safety of activated recombinant factor VII (rFVIIa/NovoSeven®/ NiaStase®) in severely injured trauma patients with bleeding refractory to standard treatment.
Inclusion Criteria

- Aged 18-70
- Blunt/penetrating trauma with evidence of active torso haemorrhage
- Hypotension due to hypovolemic
- Ongoing volume loading
- Acidosis
- Minimum 4U PRBC
Control™

Clinical Trial on the Effect of rFVIIa on Traumatic Blood Loss

August 2005-Sept 2008

Site selection visits: ~200 sites
Sites selected: 150
Number of countries: 32
Patients randomised: 573
• “Due to an lower mortality than anticipated (around 10% in the phase 3 trial in total compared to more than 25% in the phase 2 trial), a futility analysis was conducted to assess the likelihood of reaching a successful outcome on the primary endpoint.

• The analysis predicted a low likelihood of obtaining a positive trial outcome with the planned study population, and as a consequence, Novo Nordisk has decided to discontinue the trial.

• The decision is not due to safety concerns. The independent Data Monitoring Committee recommended continuation of the study.”

Novo Nordisk press release 2008
Summary

- Mortality and morbidity
  - No significant differences between placebo and rFVIIa
- Transfusion requirements: blunt patients (post-dosing to 24h)
  - Significant reduction in RBC (1.2 units), FFP (2.2 units) and total allogeneic blood (3.6 units)
  - No differences in platelets, fibrinogen concentrate or cryoprecipitate
- Safety
  - No statistical difference for total SAEs
Data from 560 patients.

Subjects were monitored for adverse events (AEs) after rFVIIa or placebo administration. Incidences, timing, and presence of risk factors were reported by site investigators, supported by external study monitors and overseen by an independent Data Monitoring Committee.
J Trauma. 2011 May 23. [Epub ahead of print]
Recombinant Activated Factor VII Safety in Trauma Patients: Results From the CONTROL Trial.

- No differences in overall mortality, organ system failure, or AEs, serious AEs, or medical events of special interest.
- Arterial and venous thromboembolic (TE) events and their risk factors were similar in both groups.
- The greatest risk factor for TE events was a chest injury requiring mechanical ventilation >3 days (86%).
- Four site investigator-reported MIs in the rFVIIa group of which only one met diagnostic criteria pre-established by the Data Monitoring Committee. There were no reported myocardial infarctions in the placebo group. Troponins were increased in 30% of all patients.
- The rate of acute respiratory distress syndrome was lower in the rFVIIa (3.0%) than in the placebo (7.2%) group (p = 0.022).

- rFVII associated with an imbalance of investigator-reported AMI/NSTEMI, but no increased risk for other AEs, including TE complications.
- Mortality benefit for at risk of bleeding
- Mechanism?
- Safety as long as given early
- Cheap

- Transfusion benefit in massive transfusion setting
- Known mechanism
- Safety?
- Expensive