Transfusion - Issues in Africa

Professor Kathryn Maitland
Factorial design:

3950 children with severe anaemia

- Transfusion strategies
- Long-term management

TRAnfusion and TReatment of severe Anaemia in African Children Trial
ISRCTN84086586
Severe anaemia in sub Saharan Africa: the context

- Severe anaemia- major cause of paediatric admission
- 5/1000 children < 5 years die each year of severe anaemia
- > 15% of paediatric admissions receive a transfusion
- Insufficient blood available for paediatric transfusion
- 17% of children hospitalised with severe anaemia die
  - 6-8% of deaths occur in-hospital with another
  - 10-14% dying within 6 months of admission
WHO Terminology

Severe anaemia (SA) Hb < 5-6 g/dl*

Profound anaemia: Hb < 4 g/dl

Severe and complicated anaemia: SA plus life threatening features
Pattern of usage of blood: demand

UK
- Pregnancy-related
- Children
- Surgery
- Medical
- Trauma
- Haematology

Largely elective-use
Pre-planned and predictable

Africa
- Pregnancy-related
- Children
- Surgery
- Medical
- Trauma
- Haematology

¾’s blood use: paediatric & pregnancy-related
Largely emergency use
✓ Unpredictable
✓ Highly seasonal
Supply: In SSA: < 5 units/1000 population

WHO estimates needs are > 20 units/1000 for current demand
WHO Recommendations for Paediatric transfusion

Give a transfusion (20mls/kg whole blood or 10mls/kg packed cells to

✓ all children with a Hb of ≤4 g/dl (profound anaemia)
✓ less severely anaemic children (Hb 4–6 g/dl) +features of severity

Concerns

Current recommendation developed by ‘blood safety’ committee of WHO (transfusion specialists) not by the paediatric guideline committee

• Designed to protect supplies of blood
• Not evidence based- but driven by necessity
• Evidence suggests that doctors usually ignore these
• One size fits all: leads to 30% under transfused  (Kiguli BMC Med 2015)
WHO needs transfusion?

WHO Transfusion thresholds

Stable

‘Complicated’

Brabin et al 2001: Review of evidence: Haemoglobin and relative risk of death: need for a trial
Meremikwu, M et al 2000 Cochrane review: need for a trial
Anaemia and blood transfusion in African children presenting to hospital with severe febrile illness

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Poor Tx guideline compliance:

<table>
<thead>
<tr>
<th>Anaemia</th>
<th>n (%)</th>
<th>Any transfusion</th>
<th>2 or more Tx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe: &lt; 5 g/dl</td>
<td>1002 (33%)</td>
<td>94%</td>
<td>30%</td>
</tr>
<tr>
<td>Moderate 5-7 g/dl</td>
<td>501 (16%)</td>
<td>70%</td>
<td>12%</td>
</tr>
<tr>
<td>Mild: 7-10 g/dl</td>
<td>843 (27%)</td>
<td>12%</td>
<td>1%</td>
</tr>
</tbody>
</table>

Severe anaemia group (Hb < 5 g/dl)\footnote{Importance of early transfusion}

48 hour mortality if received BTX within 8 hours =4%

- 48-hour mortality if DID NOT get BTX within 8 hours =54%
Transfusion questions

Which children should receive a transfusion?
• Current WHO guidelines have not been evaluated in clinical trials. *We don’t know if giving blood to all children with Hb <6g/dl would help.*

How much blood should be given in a transfusion?
• A quarter of children receiving transfusions remain severely anaemic and up to one third get two or more blood transfusions during a single hospital admission. *We don’t know if giving larger initial volumes of blood would help*
Transfusion RCTs
All multicentre, non inferiority trials <Hb 7 versus higher threshold

TRIC trial 1999
Adults ICU

TRIPICU trial, 2007
Paediatric ICU

TRISS trial 2014
988 Adults
Transfusion randomisations

Eligible Child >2m with Hb <6g/dl

- Profound anaemia and severe complicated
  - <4g/dl or prostration or respiratory distress or haemoglobinuria or sickle cell
    RANDOMISE (R1A)
  - 30 ml/kg whole blood transfusion
    Or 15 mls/kg if packed cells

- Uncomplicated severe anemia 4-6 g/dl
  - 4-6g/dl, no prostration, no respiratory distress, no haemoglobinuria, no sickle cell
    RANDOMISE (R1B)
  - 30 ml/kg whole blood transfusion
  - 20 ml/kg whole blood transfusion
  - 20 ml/kg whole blood transfusion
  - no whole blood transfusion
Phase II trial of standard versus increased transfusion volume in Ugandan children with acute severe anemia

Peter Olupot-Olupot¹, Charles Engoru², Jennifer Thompson³, Julius Nteziyaremye³, Martin Chebet¹, Tohru Ayukawa⁴, and Kathryn Maitland⁴,*

Abstract

Background: Severe anemia (SA, hemoglobin <6 g/dl) is a leading cause of pediatric hospital admission in Africa, with significant in-hospital mortality. The underlying etiology is often infectious, but specific pathogens are rarely identified. Guidelines developed to encourage rational blood use recommend a standard volume of whole blood (20 ml/kg) for transfusion, but this is commonly associated with a frequent need for repeat transfusion and poor outcome. Evidence is lacking on what hemoglobin threshold criteria for intervention and volume are associated with the optimal survival outcomes.

Methods: We evaluated the safety and efficacy of a higher volume of whole blood (30 ml/kg; Tx30: n = 78) against the standard volume (20 ml/kg; Tx20: n = 82) in Ugandan children (median age 36 months (interquartile range (IQR) 13 to 53)) for 24-hour anemia correction (hemoglobin >6 g/dl: primary outcome) and 28-day survival.
Main findings

All transfusions in the trial were Whole Blood

180 children: median Hb=4.2g/dl

• Initial volume received followed the randomization strategy in 155 (97%) patients.
• By 24-hours, 70 (90%) children in the Tx30 arm had corrected severe anaemia vs 61 (74%) in the Tx20 arm; $P = 0.01$).
• From admission to day 28 there was a greater hemoglobin increase from enrollment in Tx30 (global $P <0.0001$);
• Serious adverse events: **Tx30**: 1 non-fatal allergic reaction and 1 death **Tx20**: six deaths ($P = 0.12$)
Mean haemoglobin (95% confidence intervals) over 28 days by arm

<table>
<thead>
<tr>
<th>Time</th>
<th>0hrs</th>
<th>8hrs</th>
<th>16hrs</th>
<th>24hrs</th>
<th>48hrs</th>
<th>28days</th>
</tr>
</thead>
<tbody>
<tr>
<td>N Arm A:</td>
<td>82</td>
<td>73</td>
<td>76</td>
<td>77</td>
<td>76</td>
<td>70</td>
</tr>
<tr>
<td>N Arm B:</td>
<td>78</td>
<td>75</td>
<td>76</td>
<td>74</td>
<td>74</td>
<td>71</td>
</tr>
<tr>
<td>P</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>0.008</td>
<td>0.002</td>
<td>0.59</td>
<td></td>
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</tbody>
</table>

Global test of difference between the arms in change in haemoglobin from enrolment through to 28 days: p<0.0001
Certificate of Analysis?
Strengthening BTS: comes at a cost!

External Financial Aid to Blood Transfusion Services in Sub-Saharan Africa: A Need for Reflection

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Plos Med Sept 2012
Consequences of PePFar funding

✓ Improved safety of blood (HIV) – marginal gains........

Adverse consequences.....

❖ Poor regional distribution of blood through centralisation of BTS: inequity of access to blood

❖ Component preparation: costly & wasteful- preference for whole blood for emergencies has been ignored

❖ Exclusive use of low risk population (school children rather than replacement donors: huge stock outs!)
Pattern of usage - most transfusions required for emergencies
Whole blood
Viable for 30-42 days

Red cell concentrate from decantation
Viable for 30-42 days

Red cell concentrate from centrifugation
Viable for 30-42 days

Packed cell
Viable for 1 day only

WHO indicates packed cells but these are only viable for one day!!
Blood pack type and preparation

Majority of red cell concentrates have LOWER haematocrit than recommended.

Packed cells not feasible owing to short viability.
In practice

Overnight Settling of blood packs

Cold chain?
Decanted plasma-(will be discarded)
No red cell irradiation
Age of Blood?
<table>
<thead>
<tr>
<th>Age of blood</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 - 7 days</td>
<td>136 (24.2)</td>
</tr>
<tr>
<td>8 – 14 days</td>
<td>162 (28.8)</td>
</tr>
<tr>
<td>15 – 21 days</td>
<td>129 (22.9)</td>
</tr>
<tr>
<td>&gt; 21 days</td>
<td>136 (24.1)</td>
</tr>
</tbody>
</table>
Lessons learnt

• TRACT trial has been the first opportunity in Africa to highlight issues arising out of ‘strengthening BTS’
• Lack of communication between donor initiatives and users – risks lives
• ‘Strengthening’ of BTS practices using western models – consequences on
  – quality of blood, storage lesion (cold chain and storage age)
  – Access to blood for transfusion in rural areas – excess mortality but metrics not being collected
  – Lack of quality control of blood issued for transfusion.

SERIOUS HAZARDS OF TRANSFUSION

SHOT
Red cell polymorphisms in donor blood

<table>
<thead>
<tr>
<th>Red blood cell polymorphisms in Uganda</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbS</td>
<td></td>
</tr>
<tr>
<td>AA (normal)</td>
<td>1770/2123 (83.4)</td>
</tr>
<tr>
<td>AS (sickle cell trait)</td>
<td>334/2123 (15.7)</td>
</tr>
<tr>
<td>SS (sickle cell anaemia)</td>
<td>19/2123 (0.9)</td>
</tr>
<tr>
<td>$\alpha^+$ thalassaemia – n (%)</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>1181/2114 (55.9)</td>
</tr>
<tr>
<td>Heterozygote</td>
<td>792/2114 (37.5)</td>
</tr>
<tr>
<td>Homozygote</td>
<td>141/2114 (6.6)</td>
</tr>
<tr>
<td>G6PD deficiency – n (%)</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>531/597 (88.9)</td>
</tr>
<tr>
<td>Deficient$^a$</td>
<td>66/597 (11.1)</td>
</tr>
</tbody>
</table>
What happens to an ageing red blood cell?

**Cellular membrane changes**
- Reduced deformability
- Increased osmotic fragility
- Formation of microparticles

**2,3-DPG depletion**
- Increased oxygen affinity
- Decreased cytoskeletal plasticity

**ATP depletion**
- Less resistance to oxidation
- Reduced enzymatic activity
- Reduced transporter function

**Additive solution changes**
- Capillary occlusion
- Endothelial dysfunction
- Inappropriate immunomodulation
- Increased clot formation
TRACT progress

- Started in Sept 2014
- Deliberate initial slow recruitment
- Sept 2015: 1750/3954 (44%) enrolled
- Retention: At 90 and 180 days is currently 98% and 97% including deaths (primary endpoints) as retained.