Challenges of managing children with severe anaemia

Severe anaemia is a leading cause of hospital admission in children in sub-Saharan Africa. Children admitted to hospital with severe anaemia have poor outcomes, with around 9-10% dying while in hospital, and 12% dying within 6 months of admission. Children admitted to hospital with severe anaemia are also at high risk (18%) of having to be re-hospitalised within 6 months of the initial hospital discharge.

Supplies of safe blood for transfusion in sub-Saharan Africa are very limited, and not enough to meet the high demand for blood. Children and child-bearing woman receive up to 75% of all blood transfusions.

The WHO guidelines for managing common childhood illness recommend a restricted approach to blood transfusions for children with severe anaemia, to preserve the scarce resource. For children with complicated or profound severe anaemia, guidelines recommend using 20mls/kg whole blood equivalent regardless of haemoglobin level.

The evidence upon which these guidelines are based is weak. Standard formulae for transfusion volume suggest that 20mls/kg may be around 30% below what would be

Key points

• Severe anaemia is common and life-threatening for children in sub-Saharan Africa.
• There is often more demand for than supply of safe blood for transfusions in these settings.
• WHO recommendations, based on expert opinion, recommend conservative blood transfusion strategies, to preserve scarce resource and reduce risk of transfusion-transmitted infections. This includes giving children who require a transfusion 20mls/kg, which standard calculations suggest is insufficient for deficit-correction of haemoglobin (requiring ~30mls/kg).
• The TRACT trial tested whether giving children with severe anaemia liberal transfusions (30mls/kg of whole blood equivalent) improved mortality compared to those who received recommended conservative transfusions (20mls/kg of whole blood equivalent).
• Overall, there was no difference in mortality between children randomised to receive 30mls/kg compared to 20mls/kg.
• But there was strong evidence that the effect of transfusion volume varies by whether the child had a fever at the time of screening (study enrolment). Children with a fever on study entry (screening) did better with 20mls/kg, while children with no fever at study entry did better with 30mls/kg.

* Children without a fever at the time of screening (two thirds of those included in the trial) were at half the risk of dying by day 28 if they received 30mls/kg rather than standard 20mls/kg (3% vs 6% absolute risk).
* Children with a fever (>37.5°C) at the time of screening were at almost half the risk of dying by day 28 if they received 20mls/kg rather than 30mls/kg (3% vs 5% absolute risk).
• The two strategies used similar numbers of blood packs overall, as children receiving 20mls/kg were more likely to need more than one transfusion.
• Giving children who did not have a fever at the time of hospital admission 30mls/kg halved mortality compared to giving them 20mls/kg, at a cost of $20 per life-year gained.
required to correct severe anaemia to ≥9g/dl (haemoglobin deficit-correction). Adherence to the WHO guidelines on transfusion for severe anaemia is poor, as clinicians are concerned that the guidelines undertreat children. Research is needed to evaluate what volume of blood should be transfused for children admitted to hospital with severe anaemia. This briefing paper explores the results of the TRACT trial, which compared giving children liberal (30mls/kg) vs conservative (20mls/kg) transfusions of whole blood equivalent.

Did liberal transfusions improve outcomes for children with severe anaemia overall?

Haemoglobin increased more among children receiving 30mls/kg vs 20mls/kg, with mean +1g/dl greater haemoglobin at 48 hours. Haemoglobin recovered to >9g/dl faster with 30mls/kg, and new haemoglobin <4g/dl occurred less frequently. These differences are unlikely to be due to chance. However, overall, by day 28 there was no evidence of differences in haemoglobin between groups, nor were there any differences after this.

By day 28, 3% of children in the 30mls/kg group had died, compared to 5% in the 20mls/kg group. This difference is compatible with chance. There was no evidence of a difference in mortality by day 180. Around 19% of children in the 30mls/kg group and 17% in the 20mls/kg group were readmitted to hospital within 180 days. This difference is also compatible with chance. Just over one in four children experienced one or more severe adverse events, with no evidence of difference between the groups. Severe adverse events were mainly readmission to hospital.

Did the effect of liberal transfusions vary by fever at the time of screening?

There was one pre-specified subgroup where there was evidence of substantial variance with the overall result (also called heterogeneity) in the effects of 30mls/kg vs 20mls/kg on 28-day mortality: this was documented fever by a digital thermometer (axillary temperature >37.5°C) at the time of screening. There was very strong evidence (heterogeneity p-value=0.001) that the results varied by whether children had a fever or not, which is unusual in clinical trials and therefore very likely to be a real result.

1943 (61%) children did not have a fever (ie had temperature of ≤ 37.5°C) at the time of screening. Among these children, there was a large difference in 28-day mortality between those randomised to 30mls/kg vs 20mls/kg. In the 30mls/kg group 3% had died by day 28, compared to 6% in the 20mls/kg group. Having 30mls/kg more than halved 28-day mortality compared to having 20mls/kg among children without a fever. This difference is very unlikely to be due to chance.

1253 (39%) children did have a fever (>37.5°C) at the time of screening. Among these children there was also a difference in 28-day mortality between those randomised to 30mls/kg vs 20mls/kg. In the 30mls/kg group 5% had died by day 28, compared to 3% in the 20mls/kg group. Having 30mls/kg nearly doubled 28-day mortality compared to having 20mls/kg among children with a fever at the time of screening. This difference is unlikely to be due to chance.
In children without fever at screening, the benefit of giving 30mls/kg rather than 20mls/kg is exactly what the trial hypothesised overall – 20mls/kg is insufficient to correct the anaemia deficit in these children in whom anaemia is the main illness, and giving more blood reduces their chances of dying. Among children with a fever, the mechanism for the harmful effect of 30mls/kg is unclear. There was no evidence that any other pre-specified subgroups benefited more from higher or lower volumes of transfusion.

Resources used by the two strategies
12% of children in the 30mls/kg group required further transfusions, compared to 19% of children in the 20mls/kg group. This difference is not compatible with chance. While the initial transfusions in the 30mls/kg group required more blood packs, because fewer children in this group needed additional transfusions, the number of blood packs used in both groups was very similar.

The main contribution to costs were hospital stay, blood transfusions and haemoglobin tests. Total costs per child were $80.62 in the 30mls/kg group and $81.97 in the 20mls/kg group. Years of life gained over 180 days were marginally lower in the 20mls/kg group. For the subgroup without fever, the increased costs of 30mls/kg (compared to 20mls/kg) was only $20 per life-year gained which is highly cost effective. For the subgroup with fever, 30mls/kg was more costly and less effective than 20mls/kg.

What do these results mean for treating children with complicated severe anaemia in sub-Saharan Africa?
These results mean that children admitted to hospital with complicated severe anaemia should have their temperature tested upon admission:
• Those without a fever should be given a blood transfusion of 30mls/kg
• Those with a fever should be given a blood transfusion of 20mls/kg

This strategy could save lives, without substantially increasing the number of blood packs required, as children who receive the higher initial volume are less likely to require additional transfusions. Giving children without fever a transfusion of 30mls/kg rather than 20mls/kg is cost effective, with incremental costs of only $20 per life year gained.

If implemented widely, this could save the lives of many children with severe anaemia. There may be some challenges in implementing this strategy, including the need for accurate ways to measure the volume of blood being given (eg gauged burettes).
What are the implications of the results on characteristics of donor blood for transfusion services?

44% of children in this part of the TRACT trial received whole blood in their first transfusion, with the rest receiving either packed or settled red blood cells. Average blood storage time was 12 days. There was no evidence that characteristics of the blood pack used (pack haemoglobin, type of blood pack or blood age) were associated with 28-day or 180-day mortality.

These findings are important for a number of different reasons. First blood transfusion services in most African countries do not take out white blood cells (leucocyte-reduction) owing to the costs. Leucocyte-reduction is standard elsewhere, where it is considered to make longer stored donor blood safe and reduce transfusion reactions. We found no evidence that longer storage times resulted in poor outcomes and we observed very few transfusion reactions. Whole blood has been replaced in some countries by packed cells at substantial costs to Blood Transfusion Services. Whole blood is more appropriate to replace volume for the two key user groups of Blood Transfusion Services in Africa (young children and pregnant woman). The fact that there were no safety concerns in children receiving whole blood (ie we observed no episodes of ‘heart overload’ and no evidence the whole blood had worse outcomes (28-day or 180-day mortality)) means that it can be safely used for paediatric transfusions in Africa.

This suggests that component preparation, which has a substantial cost, is not essential for safe transfusion practice.

Implications for future research

Further research is needed to explore the reasons why the effect of transfusion volume varied by whether children had a fever or not. A substantial proportion of children in TRACT (18%; nearly 1 in 5) were readmitted to hospital within 180 days. Future trials should focus on strategies to prevent the need for readmission.

Further research to estimate the potential cost-savings from providing whole blood rather than packed/settled cells could provide useful guidance for Blood Transfusion Services.

Recommendations

- Children with complicated severe anaemia should have their temperature taken at the time of admission to hospital
  - Children without a fever at time of admission should receive transfusions of 30mls/kg whole blood equivalent
  - Children with a fever at time of admission should receive transfusions of 20mls/kg whole blood equivalent
- Hospitals should ensure they can measure the temperature of children being admitted, and measure the volume of blood they are giving (eg through the use of gauged burettes)
- Component preparation of blood is not essential for safe transfusion practice

Further reading


Immediate vs no immediate transfusion strategies for children with uncomplicated severe anaemia. TRACT briefing paper.

Acknowledgements

This briefing paper was written by A South, S Walker, D Gibb and K Maitland on behalf of the TRACT trial team.

The TRACT trial was funded by the UK Medical Research Council (MRC) [MR/J012483/1].