Liberal *vs.* Conservative Approach to Timing of Blood Transfusion in Severely Anemic Children

***Source Citation*:** Maitland K, Kiguli S, Olupot-Olupot P, Engoru C, Mallewa M, Saramago Goncalves P, *et al*. Immediate transfusion in African children with uncomplicated severe anemia. N Engl J Med. 2019;381:407-19.

***Section Editor*:** ABHIJEET SAHA

SUMMARY

In this open label trial, children aged 2 months to 12 years with uncomplicated severe anemia received immediate blood transfusion in the intervention group while in the control group, immediate transfusion was withheld. Children in the intervention group were further randomized to receive higher (30 mL/kg whole blood/ 15 mL/kg packed cells) or lower (20 mL/kg whole blood/ 10 mL/kg packed cells) volume, administered immediately after enrolment. Hemoglobin (Hb) was measured 8-hourly, and an additional transfusion using the original volume was given if the criteria for transfusion were met. For children requiring further transfusions, only 20 mL/kg whole blood (or 10 mL/kg packed cells) was used. In the control group, transfusion with 20 mL/kg of whole-blood equivalent was triggered by new signs of clinical severity or a drop in Hb to below 4 g/dL during 8-hourly monitoring, The primary out-come was 28-day mortality. Three other randomizations investigated transfusion volume, post-discharge supplementation with micronutrients, and post-discharge prophylaxis with trimethoprim–sulfamethoxazole.

A total of 1565 children underwent randomization, with 778 assigned to the immediate-transfusion group and 787 to the control group. The children were followed for 180 days, and 71 (4.5%) were lost to follow-up. During the primary hospitalization, transfusion was performed in all the children in the immediate-transfusion group and in 386 (49%) in the control group (median time to transfusion, 1.3 hours *vs*. 24.9 hours). The mean (SD) total blood volume transfused per child was 314 (228) mL in the immediate transfusion group, and 142 (224) mL in the control group. Seven children (0.9%) in the immediate-transfusion group and 13 (1.7%) in the control group died by 28 days (HR 0.54; 95% CI 0.22, 1.36; *P*=0.19), and 35 (4.5%) and 47 (6.0%), respectively (HR 0.75; 95% CI, 0.48, 1.15) by 180 days, without evidence of interaction with other randomizations or evidence of between-group differences in readmissions, serious adverse events, or hemoglobin recovery at 180 days. The authors concluded that there was no evidence of differences in clinical outcomes over 6 months between the children who received immediate transfusion and those who did not.

COMMENTARIES

Evidence-based Medicine Viewpoint

Relevance: Severe anemia (defined as hemoglobin less than 6 g/dL), is a frequent cause of childhood hospitalization in many African countries [1,2]. The traditional approach in such children is to offer blood transfusion only if hemoglobin (Hb) is less than 4 g/dL, or when Hb is 4-6 g/dL in the presence of clinical features like dehydration, shock, altered sensorium, cardiac failure, breathing difficulty, hemoglobinuria, or underlying sickle cell disease. This somewhat conservative approach is based on the World Health Organization (WHO) recommendations [3], which are based on dated observational studies with methodological limitations. This randomized clinical trial [4] compared a liberal (*i.e.*, immediate blood transfusion) *versus* conservative (*i.e.,* as per WHO guidelines) approach in children with uncomplicated severe anemia (defined as mentioned above). ***Table* I** outlines the characteristics of the trial [1].

Critical appraisal: ***Table* II** outlines the methodological aspects of the trial. Overall, the methodological quality was high. The trial protocol was published [5], and there are no deviations discernible. However, some points require careful consideration.

In this trial [4], the mortality rate in both arms was far lower than the anticipated baseline mortality rate of 9%. Thus, although there was approximately 50% lower mortality in the intervention arm (0.9% compared to 1.7%), the trial remained underpowered to confirm if a true

TABLE I OUTLINE OF THE TRIAL

Parameter	*Comments*
Clinical question	Although a clinical question in the traditional PICOT format was not mentioned, it could be stated as: "In children with severe uncomplicated anemia (Hb 4-6 g/dL) without signs of clinical severity (*P=Population*), what is the efficacy, safety and cost (*O=Outcomes*) of immediate blood transfusion (*I=Intervention*) compared to no immediate transfusion (*C=Comparison*) over a period of 6 months (*T=Time frame*)?"
Study design	Randomized controlled trial with individual participants randomized 1:1 to two groups *viz* immediate transfusion versus no immediate transfusion. The former were further randomized to receive either 20 mL/kg or 30mL/kg of whole-blood equivalent.
Study setting	Three hospitals in Uganda and one hospital in Malawi.
Study duration	September 2014 to May 2017.
Inclusion criteria	Children (2 mo to 12 y) admitted with 'severe uncomplicated anemia', defined as Hb 4-6 g/dL without signs of clinical severity (altered sensorium, respiratory distress, or acute hemoglobinuria) or pre-existing sickle cell disease.
Exclusion criteria	Children with prior renal or hepatic failure, malignancy, congenital cardiac defect, trauma/burns, or those requiring surgical intervention. Exclusively breastfed babies were excluded without explanation.
Intervention and Comparison groups	*Intervention*: higher (30 mL/kg whole blood/ 15 mL/kg packed cells) or lower (20 mL/kg whole blood/ 10 mL/kg packed cells) volume, administered immediately after enrolment. *Control*: transfusion (20 mL/kg whole blood/ 10 mL/kg packed cells) only if Hb dropped below 4 g/dL and/or they developed clinical signs of severity.
Outcomes	*Primary*: Death occurring within 28 days after randomization. *Secondary*: death within 48 h, 90 days or 180 days of randomization; proportion in whom Hb declined <4 g/dL during admission; proportion in whom Hb declined <6 g/dL after discharge; proportion in whom Hb increased >9 g/dL (although time point of measurement was not specified); proportion re-hospitalized; number developing transfusion reactions; number developing serious adverse events; cost of management; cost-effectiveness.
Follow-up protocol	Clinical examination was done at baseline (randomization), 30 min, 1 h, 90 min, 2 h, 4 h, 8 h, 16 h, 24 h, and 48 h. The parameters evaluated were not specified. Hb was measured at 8 h, 16 h, 24 h, 48 h, and additionally if there was (undefined) clinical worsening. Clinical and Hb examination were done after discharge on days 28, 90 and 180.
Sample size	*A priori* sample size calculation was performed for a superiority trial, to detect 50% decline in 28-day mortality from an expected baseline 9% to 4.5%. Allowance was made for an attrition rate of 6%.
Data analysis	Intention-to-treat (ITT) analysis was undertaken, analyzing participants in the same groups to which they were randomized. However, the outcome assignment to drop-outs was not specified.
Comparison of groups at baseline	The groups were comparable at baseline with respect to median age, gender, anthropometric measurements, clinical features (vital signs, fever, signs of shock/dehydration), laboratory parameters (proportion with HIV, malaria, positive blood culture, CRP and lactate level). Proportions with previous transfusions and underlying sickle cell disease were also calculated. In addition, after the trial was completed, genotyping was undertaken to identify unknown sickle cell disease.
Summary of results (Intervention *vs* Comparison groups)	*Primary outcome*: • Death occurring within 28 d : 7/778 *vs* 13/787; OR 0.54 (CI 0.22, 1.36) *Secondary outcomes*: • Death within 48 h: 0/778 *vs* 2/787; OR 0.20 (CI 0.01, 4.21) • Death within 90 d: 24/778 *vs* 31/787; OR 0.78 (CI 0.45, 1.33) • Death within 180 d: 35/778 *vs* 47/787; OR 0.74 (CI 0.47, 1.16) • Proportion in whom Hb declined <4 g/dL during hospitalization: 11/778 *vs* 309/787; OR 0.03 (CI 0.02, 0.05)

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Parameter	*Comments*
	• Proportion in whom Hb declined <6 g/dL after discharge: 106/778 *vs* 142/787; OR 0.73 (0.56, 0.94) • Proportion in whom Hb increased >9 g/dL: 399/778 *vs* 43/787; OR 11.73 CI 8.69, 15.84) • Proportion re-hospitalized: 123/778 *vs* 113/787; OR 1.09 (CI 0.84, 1.40) • Number developing transfusion reactions: 0/778 *vs* 0/787; OR 1.0 (CI 0.02, 51.05) • Number of allergic reactions: 6 *vs* 2 (but no. of children not specified) • Cost of management: USD 72.1 *vs* USD 66.5 • Cost-effectiveness: Incremental cost-effectiveness ratio (ICER) not presented. However, the life years gained over 6 months were not different in the two groups.

TABLE II CRITICAL APPRAISAL OF TRIAL METHODOLOGY

Criteria	*Conclusion*	*Comments*
Generation of random sequence	Adequate.	The sequence (to allocate participants into the immediate *versus* no immediate transfusion groups) was generated using a computer program; although, details were not provided. Variable block sizes were used though the range of block sizes was not mentioned. The method for further randomizing those in the immediate transfusion groups to higher or lower transfusion volumes was not mentioned.
Allocation concealment	Adequate	Opaque, sealed envelopes contained the main allocation. However, the method for concealing the subsequent randomization to higher or lower transfusion volumes was not mentioned.
Blinding	Inadequate	Clinicians evaluating clinical outcomes were unblinded. Although the investigators reported that the laboratory tests were performed in a blinded fashion, this seems unlikely as Hb was done at the bedside. The participants/family members were not blinded.
Completeness of reporting	Adequate	All randomized participants were included in the primary intention-to-treat analysis. The required sample size was fulfilled for this. Detailed description of participants who dropped out were provided. However, cost-effectiveness was not formally calculated.
Selectiveness of outcome reporting	Adequate	Almost all relevant outcomes (clinical and lab) were reported.
Overall impression	Low risk of bias	

difference existed. The investigators acknowledged this issue, explaining that screening of children for possible enrolment in the trial was ceased when blood was unavailable for transfusion. Although this is a reasonable explanation, it raises the problem of logistic feasibility. Even if immediate transfusion had been superior, it seems unlikely that eligible children could/would get transfused on account of limited supplies of blood. This gap between research and practice needs to be addressed before the research findings could be implemented.

The investigators did not report the cause of severe anemia in the enrolled children. Although it could be argued that this may not affect the internal validity of the study, it is important to determine comparability between the study arms. It is also interesting to wonder how/why children with Hb <6 g/dL were relatively stable. This suggests that they were suffering from chronic anemia related to underlying disease, since severe malnutrition was present in very few (<4%) enrolled children. This is also borne by the fact that after the study, sickle cell disease was confirmed in a significant proportion of the children. Further, it appears that three-quarters of the control group children who received transfusion had a drop in Hb while under observation, suggesting ongoing blood loss or

hemolysis, neither of which were investigated further. It is also somewhat unusual that nearly a quarter of the children had received transfusion prior to the current illness, yet were not investigated further.

The WHO clinical practice guidelines for medical interns [6] prescribes 5 mL/kg of packed cells or 10 mL/kg whole blood in children with severe uncomplicated anemia; although, the handbook prescribes larger volume [3]. The first transfusion is recommended rapidly to restore oxygen carrying capacity, whereas subsequent transfusions (if required.) should not exceed 5 mL/kg/h. Oral or intravenous frusemide in the dose 1 mg/kg is mentioned if there is likelihood of circulatory overload. The transfusion protocol used in this trial [4] was not described; hence, the rate of transfusion and duration cannot be ascertained. This is especially important considering that not a single one of over 1000 transfused children developed transfusion-related fluid overload or lung injury, despite the deliberate avoidance of frusemide midway. Similarly, only eight children had an allergic reaction. These impressive findings beg for more data on how this was achieved.

In the majority of resource-limited settings, especially sub-Saharan Africa, most blood transfusions are administered as whole blood. In contrast, developed healthcare systems prefer component transfusions with packed red cells [7,8]. This is related to potential circulatory overload with whole blood, and benefit of use in multiple patients when components are used. However, there are logistic challenges to fractionate blood in most developing country settings. A recent systematic review [9] examined 14 national transfusion practice guidelines published in African countries. Among those covering the pediatric age group, three recommended transfusing packed cells, whereas two permitted either to be used. However, none of these guidelines provided a basis for the recommendation. It appears that although component transfusion is preferred despite the lack of robust supporting evidence, it is often logistically infeasible. The issue is important in this trial [4] because facilities existed for both whole blood as well as packed cell transfusion. In fact, almost half the children transfused (in either group) received packed cells. However, the basis for deciding which individual child would receive whole blood (*versus* packed cells) was not clarified. The investigators have not reported subgroup analysis to judge the relative efficacy and safety, within as well as between groups.

Although the trial showed a distinct inter-group difference in Hb level during the first 48 hours, the gap narrowed to clinically insignificant values at the follow-up visits on days 28, 90 and 180. Unfortunately, the figures in the publication [4] did not clarify whether this happened only to transfused control group children, or to all in the control group. There is also no ready explanation about why the transfused children showed increase in Hb from around 5 g/dL at 48 hours to nearly 9 g/dL by day 180.

The investigators reported a statistically significant difference in the overall duration of hospital stay between the groups, with a day less hospitalization in those who were transfused immediately. However, this outcome was not specified *a priori*, and appears to a *post hoc* analysis. The investigators did not compare the outcomes among those receiving higher *versus* lower transfusion volume in the immediate transfusion group; hence, this aspect cannot be appraised.

Although cost-effectiveness was expected to be reported, the investigators undertook a cost minimization exercise, showing that the total cost of conventional transfusion was approximately USD 5.6 less than the cost of immediate transfusion. Calculation of the incremental cost-effectiveness ratio (ICER) would have been more useful. But since the gain in life years was the same in both groups, the analysis would have favored the conservative approach. In terms of costs, it is intriguing that mean cost of hospitalization over 4-5 days was merely (approximately) USD 30. This is especially remarkable considering the sickness level of the children, and that almost two-thirds had malaria. It is even more remarkable considering that the costs of measuring Hb 5 times during hospitalization was approximately one-third as much as the total hospitalization cost. These observations suggest that the actual cost of hospitalization may have been higher than represented, thereby widening the gap between the two groups.

Extendibility and Conclusion: This trial did not find overall benefit of immediate blood transfusion over traditional conservative approach. However, there are several methodological issues requiring clarification, to understand the true value of this study. There are several major differences from the trial setting and the Indian setting. These include the relatively high burden of uncomplicated severe anemia in sub-Saharan Africa, underlying causes of severe anemia (chronic disease with a high burden of malaria, but relatively uncommon severe malnutrition), underlying sickle cell disease in a significant proportion, and management protocols to pragmatically manage severe anemia in children. In India, the National Family Health Survey-4 [10] used a cut-off of 11 g/dL to identify anemia in over half of the

children younger than 5 years, highlighting the stark difference from sub-Saharan Africa. Further, most hospital protocols in Asian countries correct anemia below 7 g/dL using packed cells, with careful monitoring and interventions to prevent fluid overload [11]. For these reasons, the findings in this trial [4] may not be directly applicable to Indian context.

Funding: None; *Competing interests*: None stated.

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Pediatrician's Viewpoint

The prevalence of childhood anemia in India has remained high over the last few decades and as per NFHS-4 estimates, 58% children under 5 years of age anemic and 2% have severe anemia [1]. Restrictive red blood cell (RBC) transfusion strategy at a hemoglobin cut-off level of 7 g/dL has been advocated to reduce transfusion requirements without significant increase in adverse effects [2].

In the current multicenter study, Maitland, *et al.* [3] have demonstrated that immediate transfusion led to early hemoglobin recovery than the triggered transfusion strategy, and also reduced the number of children who developed profound anemia (Hb <4 g/dL) but the hospital readmission rates did not differ in the two groups. In the trial settings, clinical and Hb monitoring was an inbuilt component of the treatment strategy, which is usually not possible rigorously in the actual clinical and field settings. This also contributes significantly to the associated mortality in these children.

Considering the fact that India still has a very high prevalence of malnutrition and a large burden of children with severe acute malnutrition [4], unlike that reported by Maitland *et al.* [3], wherein it has been shown that early transfusion within the first 48 hours of admission has less adverse effects and mortality than RBC transfusion later during the course of management, it seems prudent to perform immediate transfusion in children with uncomplicated severe anemia.

Despite the rigorous trial design, there were patients lost to follow-up. In day-to-day clinical practice in the resource constrained settings with patients coming from far off distances, it is extremely difficult for the treating clinicians to ensure follow-up, and it will be a challenge to closely monitor such children with severe anemia who are discharged without transfusion and may decompensate in the community setting.

In the current study, there is no mention of anti-helminthic treatment received by any of the participants. In settings with a high burden of helminthic and parasitic infestations, if left untreated, anemia may recur, which may be a significant contributor to the readmission rates to the hospital; the current study was not able to find a difference in the readmission rate in the two groups.

Although, the immediate transfusion strategy may overburden the blood bank resources, the benefits of improved survival in children with severe anemia may outweigh this burden.

Funding: None; *Competing interests*: None stated.

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