

Improving blood transfusion safety in resource-poor countries: a case study of using leucocyte reduced blood in Uganda

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Abstract

Background: The majority of blood transfusion safety strategies recommended by the WHO for resource-poor countries focus mainly on reducing the risk of transfusion-transmitted infections (TTIs). Other technologies such as leucocyte reduction may represent complementary strategies for improving transfusion safety.

Objective: To evaluate the role of using leucocyte reduced blood in a resource-poor country.

Methods: Pre-storage leucocyte reduced (LR) red blood cells (RBCs) were specially prepared for the Tissue Oxygenation by Transfusion in severe Anaemia and Lactic acidosis (TOTAL) study, at the Uganda Blood Transfusion Services from February 2013 through May 2015. Quality control tests were performed to evaluate the procedure, and the incremental cost of an LR-RBC unit was estimated.

Results: A total of 608 RBCs units were leucocyte reduced. Quality control tests were performed on 55 random RBCs units. The median (IQR) residual leucocyte count was 4 (0.5-10) WBC/uL, equivalent to 1.8×10^6 WBC per unit. The estimated incremental unit cost of leucocyte reduction was \$37 USD per LR RBC unit.

Conclusion: Leucocyte reduction of blood in a resource-poor country is doable although relatively costly. As such, its value in resource-poor countries should be weighed against other transfusion safety propositions.

Keywords: Blood transfusion safety; leucocyte reduction; resource-poor countries.

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Background

Several blood transfusion safety strategies have been recommended for resource-poor countries, such as donor serological screening for transfusion-transmitted infections, [mainly for human immunodeficiency virus (HIV), hepatitis B and C (HBV and HCV) and syphilis], donor selection, deferral strategies and laboratory screening for malaria of all blood donations^{1,2}. Others include malaria chemoprophylaxis after transfusion, especially for the most vulnerable populations such as pregnant women³. However, these interventions focus mainly on reducing transfusion-transmitted infections (TTIs). Moreover, some of these recommended strate-

gies such as malaria testing are not implemented in endemic areas, for cost implications⁴.

Other technologies such as nucleic acid testing (NAT), leucocyte reduction and pathogen reduction (PR) which still remain largely unaffordable to most resource-poor countries may represent complementary strategies to improving blood transfusion safety in such settings.

The prevention of undesirable consequences resulting from recipient exposure to donor leucocytes is the main reason for leucocyte reduction (LR) of blood products. In modern transfusion practice, LR is achieved using high performance leucocyte reduction filters which can remove 4 logs or higher of donor leucocytes. As a result, most of LR blood units may have less than 10^6 residual leucocytes^{5,6}. The filters contain filtration media with very small size pores that impede leucocyte passage, but allow the RBCs to traverse, due to their higher deformability⁷.

LR procedure is highly effective in decreasing events related to recipient exposure to donor leucocytes namely: febrile non-hemolytic transfusion reactions (FNHTR), human leucocyte antigen (HLA) allo-immunization and

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the transmission of leucotropic viruses, such as cytomegalovirus (CMV), Epstein–Barr virus (EBV), human T lymphotropic virus (HTLV)-I/II, and human herpes virus-8 (HHV-8)⁸.

The risk of these adverse events is relatively high, due to the high burden of some of the leucotropic viruses in Uganda. The sero-positivity of HHV-8 in the Ugandan donors has been estimated to be 40%⁹, although the risk of HHV-8 transmission through blood transfusion is about 2% to 4%,^{10,11}. While the sero-prevalence of HTLV-1/2 in Uganda is 0.5%¹², of CMV (IgM) among Kenyan donors is 3.6%¹³, and that of EBV (IgG) among Ghanaian donors is 20%¹⁴. In Uganda, FNHTR accounts for 49% of all acute transfusion reactions in the general patient populations where the overall incidence of acute transfusion reactions is 9.6%¹⁵, while among cancer patients, the incidence of FNHTR is 5.3%¹⁶. Although the prevalence of HLA-allo-immunization in Uganda is unknown, elsewhere its prevalence of about 20 – 50%^{17,19}. Whereas FNH reactions may be of less clinical concern, allo-immunization to HLA antigens may complicate the care of organ transplantation patients or those who may require chronic transfusion therapy, such as sickle cell anaemia and certain cancer patients. Among such patients, the use of LR blood products as a complement to routine serological screening may mitigate these complications.

Resource-poor countries therefore need to further explore practical approaches to improve transfusion safety, since current strategies that mainly focus on screening for transfusion-transmitted infections (TTIs) may not solely assure safe blood transfusion. This case study evaluates the role of using leucocyte reduced blood in order to improve blood transfusion safety in resource poor-countries.

Methods

Study design

This was a case study of the use of LR blood for transfusion in Uganda. The study was nested in a large clinical trial; the Tissue Oxygenation by Transfusion in severe Anaemia and Lactic acidosis (TOTAL) study.

Study setting and study population

The study participants of the Tissue Oxygenation by Transfusion in severe Anaemia and Lactic acidosis (TOTAL) study were children aged 6 to 60 months with severe anaemia (haemoglobin < 5g/dL) and hyperlactatemia (blood lactate level > 5mmol/L), requiring urgent blood transfusion. The design and setting of that trial has been reported previously¹⁸. The ethics committee of the funding agency of the TOTAL study stipulated that blood products were to be leucocyte reduced.

Data collection

Blood was collected from the donation room at the Uganda Blood Transfusion Services (UBTS) centre, based at Nakasero, from known group O repeat voluntary donors, confirmed to be non-reactive for TTIs. All RBCs units were screened and found to be non-reactive for HIV, HBV, HCV and syphilis – the TTIs that are routinely tested for by UBTS. Commercially available LR blood collection bags; Leukotrap®WB, Haemone-tics, shown in figure 1, were used. Pre-storage leucocyte reduced packed RBCs units suspended in additive solution were prepared in accordance with the product manual by two laboratory staff dedicated to the TOTAL study. Within 8 hours of collection, units were filtered at room temperature, centrifuged at 1890 rpm for nine minutes, plasma separated, and preserved in additive solution. The RBCs units were refrigerated on the same day of collection at 1°C to 6°C and maintained in a study-specific inventory, both at Nakasero and the study site hospital, Mulago.



Figure 1: Leukotrap® WB blood bag from Haemonetics®

To ascertain that the process of leucocyte-filtration was successful, we performed quality control tests on 55 random blood units, between 14th February 2014 and 15th May 2015. At the bed-side; prior to the transfusion of the individual units used for quality control tests, 2mls of blood each were sampled from a sub-set of 55 LR RBCs units using a sample-site coupler, and complete blood count (CBC) were done using the Sysmex automated haematology analyzer (XN-20, Sysmex Corporation, Kobe, Japan), to determine the residual leucocyte count. We defined a failed filtration as a blood unit that failed to start filtration within five minutes of being suspended and /or would filter very slowly (for >30 minutes) and incompletely. We regarded a residual leucocyte count above $11 \cdot 1$ WBC/uL (equivalent to $>5 \times 10^6$ WBCs per unit) for successfully filtered units as not meeting international standards for LR.

The cost estimates was done using the unit cost of the blood bag, their shipment as well as operational and administrative costs at the UBTS centre. The study budget provided only \$ 18, 000 to the UBTS to support operational and administrative costs, while the blood bags were procured at a unit cost of \$48 USD (blood bag plus shipment).

Statistical analysis

The data on quality control CBCs were entered and analyzed using computer software; Excel 2010, Microsoft Corp., Redmond, WA. Continuous data were summarized with median and interquartile range (IQR).

Ethical considerations

Ethical approval was obtained from the School of Medicine Research Ethics Committee of Makerere University (REF no.2012-169), the Uganda National Council for Science and Technology (HS 1283), and the Human Research Committee of the Massachusetts General Hospital (2012P000865/MGH). The study was registered at Clinical trials.gov (NCT01586923).

Results

Between January 2013 and May 2015, a total of 608 units of red blood cells were leucocyte reduced at the Uganda Blood Transfusion Services (UBTS) centre, Nakasero, Kampala. Figure 2 summarizes the fate of the blood units; of the 608 units, 596 (98%) units were filtered successfully and sent to the Acute Care Unit (ACU) Mulago hospital for transfusion in the TOTAL trial. The rest (12 units) were unusable for transfusion for reasons of poor/failed filtration or being HBV and HCV sero-positive at screening, five of whom were for failed filtration. Another 12 units filtered successfully, but had residual leucocytes counts above $11 \cdot 1$ WBC/uL; the highest being 130/uL.

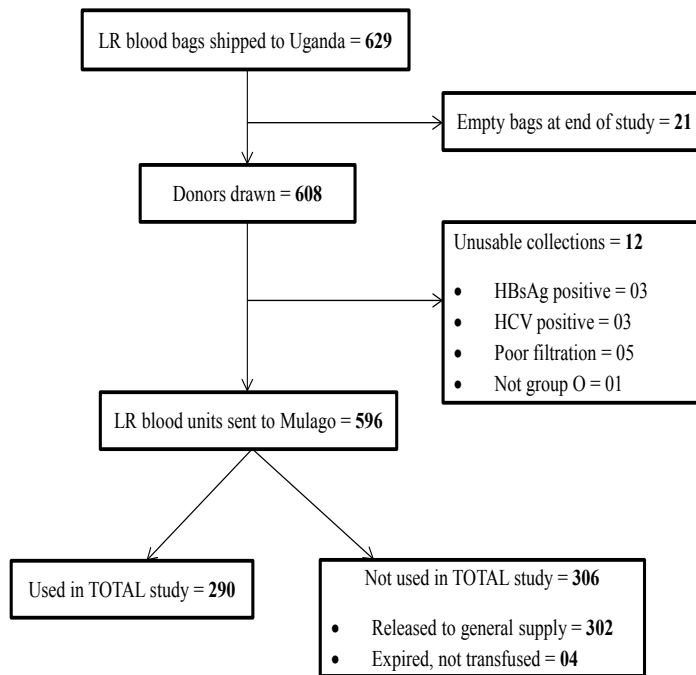


Figure 2: Outcome of leucocyte reduced blood units in Kampala, Uganda (n=608)

Quality control testing for the leucocyte reduced blood units

The median (IQR) residual leucocyte count from LR RBCs units was 4.0 (0.5-10) WBC/uL; equivalent to 1.8×10^6 WBC per unit (acceptable residual WBC counts in other jurisdictions is less than 5×10^6 per unit in USA and 1×10^6 per unit in Europe). The median (IQR) haemoglobin of the RBC units was 18.1 (16.7-19.4) g/dL.

Incremental unit cost estimate

We estimated the incremental unit cost of performing leucocyte reduction as follows: The incremental labor cost was \$0, since we did not hire new staff. The operational and administrative costs at the UBTS centre – Nakasero such as booking donors and maintaining separate inventory was approximately \$18,000 USD for the two years study period, during which 608 LR–RBCs units were processed, giving a unit cost of \$29 per bag. The cost of each LR blood bag plus shipment was \$48 USD. Thus the unit cost of each bag was \$48 plus \$29 = \$77 USD per LR–RBC unit. Therefore, the incremental unit cost of performing leucocyte reduction is \$77 USD minus \$40 USD (the estimated routine cost of preparing non-LR blood¹) = \$37 USD. As a result,

based on this estimate and the WHO estimate of a non-LR unit, the price of a LR–RBC may be approximately double that of a non-LR unit.

Discussion

The results of our case study on the role of using leucocyte reduced blood in Uganda suggest that it is feasible to prepare LR blood in a resource-poor setting. This requires training of local laboratory staff in leucocyte reduction technology, procurement of appropriate blood bags with leucocyte filters as well as quality control monitoring of the process. Furthermore, the incremental unit cost of preparing one unit of leucocyte reduced RBCs is approximately \$37 USD, in excess of \$40 USD for non-LR blood, as estimated by the World Health Organization (WHO)¹.

In most developing countries, the main focus of blood transfusion safety over the past decades has been prevention of TTIs (HIV 1 & 2, HBV, HCV and syphilis) using serological screening. Much remains to be done, since high rates of sero-positivity for these TTIs in some settings persist (i.e. 1.08%, 3.70%, 1.03% and 0.90%, for HIV, HBV, HCV and syphilis respectively)². Notably, less attention has been given to reducing other risks

such as recipient exposure to donor leucocytes, mainly due to cost constraints. However with the increasing blood transfusion demand, there is need and room to consider complementary or alternative technologies, to further improve safety. Priority would be patient categories at increased risk of transfusion related adverse events, such as sickle cell anaemia (SCA) and cancer patients. As such, the use of LR blood for high risk patient populations, combined with the current TTIs prevention strategies may prove beneficial and worth considering. This approach of optimizing the technology to specific sub-groups of transfusion recipients has been termed 'selective leucocyte reduction' 8. Although among Ugandan children with SCA, the risk of HHV-8 transmission appears to increase with increasing number of blood transfusion¹⁰, the protective efficacy of using LR blood in this population remains yet to be confirmed. On the contrary, there is strong evidence suggesting its protective efficacy in preventing HLA allo-immunization among cancer patients^{19,20}.

Given the potentially high risk of adverse events resulting from transfusion recipient exposure to donor leucocytes and the role of LR blood in improving blood transfusion safety, resource-poor countries should consider selective leucocyte reduction policies for cancer, SCA, organ transplant and other related high-risk transfusion recipients. However, each individual blood centre needs to determine their costs, taking into consideration the cost of leucocyte filtration bags, the incremental labor associated with hiring additional technologists to perform filtration, operational and administrative costs such as those related to equipment required for dual inventory management. All these costs may vary substantially across different settings. In Nigeria one SCA treatment centre has been reported to provide LR blood products to SCA patients²¹. This is commendable, although a lot more needs to be done to improve blood transfusion safety for such high risk patient populations.

Other new technologies such as pathogen reduction (PR) have recently become available. Whereas PR technology inactivates both DNA and RNA containing blood pathogens, as well donor leucocytes²², their cost still remains prohibitive for resource-poor countries⁴. A simple cost analysis reveals that preparing non-LR blood that includes routine serological screening for TTIs costs an average of \$40 USD per unit¹ and a minimum of \$18 in some countries. Advanced technologies

such as LR costs \$50 to \$60 USD per blood unit, while PR costs about \$60 to \$110 USD per blood unit⁴. As a result, in order to further improve blood transfusion safety in resource-poor countries, what may prove most affordable and most cost-effective is to continue using routine serological screening for TTIs, then prioritize the use of new and complementary technologies such as LR and probably PR (as they become affordable), for a few selected patient categories.

Limitations

Study limitations included the use of an automated cell counter to estimate the residual leucocytes; which is an inferior method compared to other methods such as Nageotte chamber counting, cytopspin method or flow-cytometry²³. The latter were not accessible to us. We did not investigate the possible reasons for cases of failed filtration, nor the higher residual leucocytes counts, such as 40/uL, 50/uL and 130/uL. Whereas inherent technical problems cannot be excluded, blood donor factors such as the potential effect of sickle cell trait blood units may have accounted for cases of failed filtration. Indeed, evidence suggests that sickle trait blood products are associated with poor filtration and high residual leucocytes counts²⁴. This is a potential challenge to Leucocyte reduction technology in African settings where the prevalence of the sickle cell gene is high, such as 13.3% in Uganda²⁵. Similarly, the incremental cost estimates for LR may differ outside a study setting. Moreover, the current cost estimates were made within the study budget limits, which make the costs not entirely generalizable to other settings.

Conclusion

Leucocyte reduction of blood in a resource-poor country such as Uganda is doable although relatively costly.

Recommendation

In resource-poor countries, the role of technologies such as Leucocyte reduction in improving blood transfusion safety may be marginal, due to the costs that remain unaffordable. However, its value must be weighed against other modification propositions. For example, selective leucocyte reduction policy for specific sub-populations such as patients with cancer and SCA and other related high-risk transfusion recipients represents a complementary strategy to improve blood transfusion safety in resource-poor countries. As such, more evidence from randomized controlled studies among these patient groups is needed to confirm the utility of such a strategy.

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Conflict of interest

None declared.

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