Cost-effectiveness of leucoreduction for prevention of febrile non-haemolytic transfusion reactions

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Background. The cost-effectiveness of universal leucoreduction of blood components remains unclear. When using leucoreduced red blood cells, the decrease in the rate of febrile non-haemolytic transfusion reactions (FNHTR) is the only proven, meaningful clinical benefit, whose relationship to costs can be calculated relatively easily. The aim of this study was to evaluate the cost-effectiveness of leucoreduction in avoiding FNHTR.

Materials and methods. Data were obtained from two large tertiary hospitals in Athens, Greece, over a 4-year period (2009-2012). The incidence of FNHTR in patients transfused with leucoreduced or non-leucodepleted red blood cells, the additional cost of leucoreduction and the cost to treat the FNHTR were estimated. The incremental cost-effectiveness ratio (ICER), which is the ratio of the change in costs to the incremental benefits of leucoreduction, was calculated.

Results. In total, 86,032 red blood cell units were transfused. Of these, 53,409 were leucodepleted and 32,623 were non-leucoreduced. Among patients transfused with leucodepleted units, 25 cases (0.047%) met the criteria for having a FNHTR, while in patients treated with non-leucoreduced components, 134 FNHTR were observed (0.411%). The ICER of leucoreduction was € 6,916 (i.e., the cost to prevent one case of FNHTR).

Conclusions. Leucoreduction does not have a favourable cost-effectiveness ratio in relation to the occurrence of FNHTR. However, many factors, which could not be easily and accurately assessed, influence the long-term costs of transfusion. It is imperative to undertake a series of large, meticulously designed clinical studies across the entire spectrum of blood transfusion settings, to investigate most of the parameters involved.

Keywords: leucoreduction, febrile non-haemolytic transfusion reaction, cost-effectiveness.

Introduction

Leucocytes present in red blood cell (RBC) and platelet concentrates have been considered as a strong risk factor for serious morbidity, and even mortality, in selected group of recipients. The adverse effects of leucocyte contamination include the transmission of cell-associated infectious agents, febrile non-haemolytic transfusion reactions (FNHTR), refractoriness to platelet transfusion, graft-versus-host disease, generalised immunosuppression, and an increased rate of rejection of bone marrow or kidney transplants[1]. Leucoreduction has demonstrated its relative cost-effectiveness in specific populations of patients, such as cytomegalovirus (CMV)-seronegative patients, immunocompromised patients, patients with human leucocyte antigen (HLA) immunisation, those with haematological or oncohaematological disorders who require multiple blood transfusions, patients with congenital or acquired haematological anaemia, and patients who have suffered from FNHTR[2]. The current trend in many western countries is to apply leucoreduction to all patients, that is universal leucoreduction (ULR). The potential risk for the transmission of variant Creutzfeldt-Jakob disease through blood transfusion and the fear associated with that risk favoured the adoption of ULR. However, sound scientific evidence supporting the cost-effectiveness and

clinical benefits of this strategy is lacking[3], leading some European countries to implement leucocyte depletion only in the case of well-established indications, mainly as a means to limit costs.

In Greece, the absence of authoritative clinical guidelines concerning ULR have led to significant disparities between hospitals in patients' access to leucoreduced blood components. Given that the extension of leucoreduction to patients lacking a clear indication for leucodepleted blood products, such as single-transfused patients, is a costly, non-mandated blood safety-related policy, and its effectiveness has not been proven, our aim was to assess the cost-effectiveness of this strategy. White blood cells probably contribute to causing several, well-established, complications of allogeneic blood transfusion including FNHTR, refractoriness to random donor platelet transfusions due to HLA alloimmunisation, transmission of CMV and an increase in mortality and risk of organ dysfunction in cardiac surgery patients[3-5].

The application of ULR to prevent primary HLA alloimmunisation in patients without immediate or short-term anticipated benefit is difficult to justify[6], while in recipients who are not at risk of developing symptomatic CMV disease, the use of leucoreduced transfusions to decrease the risk of CMV infection is unclear[7]. Febrile transfusion reactions are, therefore, the only well-established adverse effects that can be prevented by the transfusion of leucoreduced blood components to groups of patients at low risk and not requiring multiple blood transfusions. On this background we compared the incidence of FNHTR in patients transfused with leucoreduced and non-leucodepleted RBC, and calculated the costs of obtaining leucodepleted blood components and treating FNHTR in two general, tertiary hospitals in Athens, over a 4-year period (2009-2012). We then calculated the incremental cost-effectiveness ratio (ICER).

Materials and methods

The study was conducted in two tertiary hospitals in Athens (Attikon University Hospital and Nikaia General Hospital). Universal pre-storage leucoreduction was the policy implemented in Attikon University Hospital. However, a universal leucoreduced inventory was not available because of a small proportion of non-leucoreduced blood components derived from other hospitals. On the other hand, the blood bank unit of Nikaia General Hospital maintained a double inventory and reserved leucodepleted RBC only for patients with a clear indication for leucoreduced blood products, namely those with a history of FNHTR, HLA alloimmunisation, platelet refractoriness, thalassaemia major, aplastic anaemia, sickle cell anaemia, leukaemia requiring multiple blood transfusions, patients for organ transplantation, patients on dialysis and in foetal/neonatal transfusions.

All transfusion-related reactions in both hospitals during the previous 4 years (2009-2012) were reviewed, recorded and re-evaluated using the established definition of FNHTR[8]. An FNHTR was defined as the occurrence of a >1 °C rise in temperature above 37 °C associated with a transfusion and for which no other cause was identifiable. Since FNHTR is a diagnosis of exclusion, in all cases considered in the study the absence of any evidence of red cell haemolysis, bacterial contamination of the product being transfused, transfusion-related acute lung injury, or underlying febrile illness was a prerequisite. FNHTR are often associated with chills and rigors. The criterion of a 1 °C increase in temperature is considered arbitrary by some authors -since the same events might lead to smaller temperature increments- who defined reactions characterised by rigors or other symptoms, but without fever, as FNHTR, due to an assumed common mechanism[9].

In the case of a suspected reaction, the transfusion was immediately discontinued, the patient was examined by the attending clinician, and the event was reported to the transfusion service personnel. Post-reaction serum, urine samples, and the transfusion container with remnants from all suspected or definite reactions were sent to the transfusion service department for analysis. The blood bank personnel proceeded to the following workup: check for clerical errors, search for evidence of intravascular haemolysis, check for evidence of blood group incompatibility via a direct antiglobulin test and reassessment of the recipient's ABO type. If the clinical presentation indicated bacterial sepsis, a Gram stain and bacterial cultures of blood product specimens were undertaken.

In suspected febrile reactions, the clinical features and results of all laboratory tests were evaluated by a transfusion medicine physician, or the attending clinician. It was crucial to ensure that the febrile event was not part of intermittent febrile episodes. If the febrile event was attributed to the patient's underlying disease, the case was not considered a transfusion reaction. Cases with unequivocal clinical events, including chills or an increase in temperature of 1 °C or more, with or without rigors or other symptoms, and reactions characterised by chills, cold or rigors, but without fever were all designated as FNHTR[10].

Cost-effectiveness analysis

The cost of a transfusion reaction was estimated, based on a previously described model[11], by taking into account the following elements: the cost of the returned unit; the cost for each laboratory workup (including direct antiglobulin tests on pre-transfusion and post-reaction specimens, an indirect antiglobulin

test on a post-reaction specimen, reconfirmation of the recipient's ABO and Rh type on pre-reaction and post-reaction specimens, ABO and Rh testing on blood from the unit, repeat cross-match tests, testing of the new unit needed to complete the transfusion order and cultures of specimens of the blood products in the microbiology laboratory); and the cost of the transfusion medicine physician's time to investigate a transfusion reaction, based on the gross salary of an internist, which is approximately € 2,451 per month (on the basis of a 40-hour working week), and on the necessary time to investigate a transfusion reaction, which was estimated to be around 30 minutes. Additional expenses included antipyretic medication administered to patients (usually 1 ampoule of paracetamol of 6.7 mL given intravenously).

The cost of preparing a pre-storage leucoreduced RBC unit was assessed by adding the cost of a technician's time to perform the pre-storage filtration (about 6 minutes), taking into account the gross salary for a technician of approximately € 1,420 per month, to the price of the pre-storage filter.

As a means to assess whether leucoreduction is a cost-effective blood safety-related policy, the ICER was calculated. The ICER is the ratio of the change in costs to the incremental benefits of leucoreduction[12], i.e., the extra cost to avoid one case of FNHTR.

Results

During a 4-year period (2009-2012), 86,032 RBC units were transfused in the two tertiary hospitals included in this study. Of these, 53,409 were leucodepleted and 32,623 were non-leucoreduced. Among patients transfused with the former blood products, 25 cases of FNHTR (0.047% or approximately 5 per 10,000 RBC units) were observed, while in patients treated with non-leucoreduced components, 134 FNHTR events were recorded (0.411% or 41 per 10,000 RBC units). In agreement with earlier studies[13,14], transfusion with leucoreduced RBC units was associated with a statistically significant lower frequency of FNHTR (odds ratio=0.11, 95% CI: 0.07 to 0.18; $p<0.001$). The frequencies of FNHTR and allergic reactions recorded in the two tertiary hospitals during the study period are shown in Table I.

The total direct cost of a collected blood unit in a public blood centre in Athens has been previously reported (€ 253.7)[15]. The estimated cost of a transfusion reaction workup (as previously described) in the blood bank unit of Attikon University Hospital plus the antipyretic medication is € 24.6 (Table II). The pre-storage RBC leucoreduction resulted in an incremental cost of € 21-31 (an average of € 26) per unit relative to the non-leucodepleted components, depending on the commercial product used.

The equation for ICER is:

$$ICER=\frac{(\text{Cost of RBC leucoreduction}-\text{Cost of non-leucoreduction})}{(\text{Effect of leucoreduction}-\text{Effect of non-leucoreduction})}$$

The cost of a leucoreduced unit consists of the standard cost to prepare an RBC unit for transfusion (€ 253.7) and the expense to complete leucoreduction (€ 26). In the case of a febrile reaction, the unit is destroyed, which necessitates the production of a new leucoreduced product. In addition, the reaction is investigated and the patient receives antipyretics leading to an extra cost of € 24.6. Thus, the overall cost of producing leucoreduced units over the entire 4-year period was calculated as follows: 53,409 units×(€ 253.7+€ 26)+25 febrile cases×(€ 253.7+€ 26+ € 24.6)=53,409×€ 279.7+25×€ 304.3=€ 14,938,497.3+ € 7,607.5=€ 14,946,104.8. Dividing the overall cost by the total number of leucoreduced units that were transfused in that period, we obtained a final estimate of the per-unit (leucoreduced) cost, i.e., € 14,946,104.8/ € 53,409=€ 279.84.

The formula for the cost of non-leucoreduced units is quite similar except that it does not contain the leucoreduction expenses to prepare a RBC unit for transfusion.

Overall cost in 4 years: 32,623 units×(€ 253.7)+134 febrile cases×(€ 253.7+€ 26+€ 24.6)=32,623× € 253.7+134×€ 304.3=€ 8,276,455.1+€ 40,776.2= € 8,317,231.3.

The per-unit (non-leucoreduced) cost was: € 8,317,231.3/32,623=€ 254.94.

The effect of treatment was defined as the number of transfusions (e.g. per 10,000 units) that were not associated with a febrile reaction. Based on the above-mentioned estimates of the incidence of FNHTR, there were 9,995 (10,000–5) cases without a febrile reaction per 10,000 leucoreduced units transfused and 9,959 (10,000–41) cases without a febrile reaction per 10,000 non-leucoreduced units transfused.

Using the calculated values in the ICER formula presented above, we obtained an estimate of the cost incurred to avoid one febrile reaction through leucoreduction:

ICER=(Cost of transfusion of 10,000 leucoreduced units–Cost of transfusion of 10,000 non-leucoreduced units)/(Number of leucoreduced units [per 10,000] without an associated febrile reaction–Number of non-leucoreduced units [per 10,000] without an associated febrile reaction)=(10,000×€ 279.84–10,000×€ 254.94)/ (9,995–9,959)=10,000×€ 24.9/36 additional individuals without a febrile reaction=€ 6,916.6 per added case without a febrile reaction.

Table I - Transfusions and related reactions (febrile and allergic) during a 4-year period (2009-2012) in two tertiary referral, general hospitals in Athens, Greece.

	2009	2010	2011	2012	4-year period
Nikaia General Hospital					
			Transfused RBC units, n (%)		
Leucodepleted RBC units	4,838 (47)	4,896 (53)	4,669 (48)	5,255 (52)	19,658 (50)
Non-leucodepleted RBC units	5,448 (53)	4,377 (47)	5,119 (52)	4,926 (48)	19,870 (50)
All RBC units	10,286	9,273	9,788	10,181	39,528
			Transfusion reactions, n (‰)		
Leucodepleted RBC units - FNHTR	2 (0.4)	6 (1.2)	3 (0.6)	5 (1.0)	16 (0.8)
Leucodepleted RBC units - Allergic	7 (1.4)	4(0.8)	3 (0.6)	9 (1.7)	23 (1.2)
Non-leucodepleted RBC units - FNHTR	29 (5.3)	26 (5.9)	32 (6.3)	27 (5.5)	114 (5.7)
Non-leucodepleted RBC units - Allergic	4 (0.7)	3 (0.7)	8 (1.6)	8 (1.6)	23 (1.2)
Attikon University Hospital					
			Transfused RBC units, n (%)		
Leucodepleted RBC units	7,519 (62)	8,007 (75)	8,385 (72)	9,840 (82)	33,751 (73)
Non-leucodepleted RBC units	4,664 (38)	2,600 (25)	3,273 (28)	2,216 (18)	12,753 (27)
All RBC units	12,183	10,607	11,658	12,056	46,504
			Transfusion reactions, n (‰)		
Leucodepleted RBC units - FNHTR	2 (0.3)	2 (0.2)	3 (0.4)	2 (0.2)	9 (0.3)
Leucodepleted RBC units - Allergic	3 (0.4)	3 (0.4)	1 (0.1)	2 (0.2)	9 (0.3)
Non-leucodepleted RBC units - FNHTR	6 (1.3)	7 (2.7)	4 (1.2)	3 (1.4)	20 (1.6)
Non-leucodepleted RBC units - Allergic	7 (1.5)	2 (0.8)	1 (0.3)	1 (0.5)	11 (0.9)
Both hHospitals					
			Transfused RBC units, n (%)		
Leucodepleted RBC units	12,357 (55)	12,903 (65)	13,054 (61)	15,095 (68)	53,409 (62)
Non-leucodepleted RBC units	10,112 (45)	6,977 (35)	8,392 (39)	7,142 (32)	32,623 (38)
All RBC units	22,469	19,880	21,446	22,237	86,032
			Transfusion reactions, n (‰)		
Leucodepleted RBC units - FNHTR	4 (0.3)	8 (0.6)	6 (0.5)	7 (0.5)	25 (0.5)
Leucodepleted RBC units - Allergic	10 (0.8)	7 (0.5)	4 (0.3)	11 (0.7)	32 (0.6)
Non-leucodepleted RBC units - FNHTR	35 (3.5)	33 (4.7)	36 (4.3)	30 (4.2)	134 (4.1)
Non-leucodepleted RBC units - Allergic	11 (1.1)	5 (0.7)	9 (1.1)	9 (1.3)	34 (1.0)

RBC: red blood cell; FNHTR: febrile non-haemolytic transfusion reaction.

Table II - Estimation of costs for a transfusion-related reaction workup and antipyretic medication.

Parameter	Value	Total cost per parameter
Antipyretic medication	€ 0.80 (×1)	€ 0.80
Direct antiglobulin test	€ 1.24 (×2)	€ 2.48
Indirect antiglobulin test	€ 5.90 (×1)	€ 5.90
Cross-match test	€ 1.83 (×3)	€ 5.49
ABO and Rh testing	€ 2.10 (×3)	€ 6.30
Physician's time (30 min)	€ 2.45 (×1)	€ 2.45
Bacterial cultures	€ 1.22 (×1)	€ 1.22
Total cost		€ 24.64

DAT: Direct Antiglobulin Test; IAT: Indirect Antiglobulin Test; Rh: rhesus.

Discussion

In costly, non-mandated blood safety-related policies, such as the ULR of RBC, physicians must choose whether to offer the novel or the conventional product. Although leucoreduced blood is of better quality than non-leucoreduced blood, the effectiveness of ULR has not been clearly demonstrated. The decrease in the rate of FNHTR is the only proven, meaningful clinical safety benefit whose relationship to costs can be calculated relatively easily when using leucoreduced blood products outside a narrowly defined subset of patients at risk. In our study, we measured the incidence of these reactions in patients transfused with leucodepleted or non-leucodepleted RBC and calculated the costs of

leucoreduction and of treating FNHTR. Based on data from two large tertiary hospitals in Athens, we found that leucoreduction was not a cost-effective strategy with regards to FNHTR. However, conclusions based only on FNHTR might be misleading, transfused leucocytes are also associated with refractoriness to random donor platelet transfusions due to HLA alloimmunisation, transmission of CMV and allogeneic blood transfusion-related immunomodulation. The potential adverse effects of this last phenomenon are being widely and intensively investigated.

Considering evidence from experimental and clinical studies, allogeneic blood transfusion-related immunomodulation is probably associated with allogeneic white blood cells. However, the existence of detrimental clinical effects of this immunodulation has not yet been established by sufficiently powered randomised clinical trials. Thus, although leucoreduced transfusions have been reported to decrease the incidence of post-operative infections in transfused surgical patients[16,17], evidence remains weak and controversial on the benefits of leucoreduction for these patients[18]. The only clinical situation in which the use of leucoreduced allogeneic RBC has been consistently shown to decrease short-term mortality is in cardiac surgery patients[19-21]. Similarly, ULR has been reported to result in less use of antibiotics, less time spent by patients in the Intensive Care Unit, and shorter overall stays in hospital, but these findings have not yet been confirmed.

ULR also has the theoretical advantage that it may avoid the transmission of unknown or known leucocyte-associated viruses, for which no testing is currently performed. The clinical relevance of this risk reduction is still debated. Moreover, the incremental cost for each unit of filtered blood could be counterbalanced by savings in logistics due to the maintenance of a simplified inventory and the standardisation of procedures resulting in minimisation of labour costs. Keeping a double inventory for transfusion medicine services could lead to an increase in outdates of RBC units because it is difficult to ensure the balance in supply of leucoreduced and non-leucoreduced units on a routine basis. However, the extent to which all these elements contribute to reducing long-term average costs of transfusion cannot be easily or accurately assessed. It does, therefore, remain unclear whether the savings achieved by filtration of RBC units really outweigh the costs.

The fact that all the aforementioned factors were not evaluated in the analysis is certainly a significant limitation of our study and does not allow definite conclusions to be drawn about the cost-effectiveness of ULR in general. Another limitation is the potential underestimation of real cases of FNHTR, although this is not likely to have influenced the cost-effectiveness analysis since, even if it did exist, there was no reason for it to differ across the transfusion groups.

In the light of European Directive 2002/98/EC[22], which requires the implementation of all precautionary measures to safeguard public health, the following questioning arises: should blood banks, which are legally responsible for blood safety, implement a safety policy targeting the elimination of all possible risks, regardless of the costs? What should be the main priority in blood safety management? Should it be the efficient use of scarce resources, or the maximal blood safety at all costs? This uncertainty opens the door to arbitrary interpretations and leads to the coexistence of two different blood safety policies. Some public hospitals have decided to provide exclusively leucoreduced RBC products, while others have elected to order this component only for well-established indications. This disparity almost inevitably results in inequitable access of patients to safe new-technology blood components.

Since 90% of all RBC products are directed to single-transfused patients, who are not known to derive a clear benefit from leucofiltration, many transfusion medicine specialists oppose ULR, arguing that the additional cost burden to the health care system cannot be justified, since its clinical benefit has not been established in the large majority of therapeutic applications[23]. Given the paucity of data on the cost-effectiveness of leucodepletion, which have mainly been derived from selected patient groups[19,20,24], and the availability of only one randomised controlled trial estimating the general costs of ULR, in which no beneficial effect of conversion from selective to universal white blood cell reduction was observed[25], ULR still remains highly controversial.

Moreover, the cost of ULR increases substantially when it is applied to all blood components. In that case, the optimal use of blood components is imperative. Blood banks, by applying ULR, produce novel products putting an additional, possibly unjustified, cost burden on the health care system. On the other hand, some practitioners do not follow the guidelines for the use of blood components strictly, because they are not convinced about transfusion risks and are also unaware of the significant cost of blood safety-related innovations. Thus, the inappropriate use of non-mandated new technology blood products can be translated into additional waste of financial resources.

It is, therefore, essential to have national guidelines defining whether leucocyte reduction should be universal or restricted to the well-known indications, considering cost in relation to clinical benefit. The real challenge to face is the proper way in which regulatory authorities can reliably determine how clinically useful and cost-effective is ULR or any other new blood technology. It is acknowledged this is not an

easy objective, since many of the parameters related to cost and clinical effectiveness cannot be assessed reliably or without speculating far beyond available evidence. However, the objective could be achieved by undertaking a series of large, meticulously designed and well-conducted clinical studies across the whole spectrum of blood transfusion settings, taking into account the various parameters that could affect the clinical and financial aspects related to this blood safety strategy. In the absence of this evidence, we consider that, in terms of safety and cost-effectiveness, the most rational approach seems to be to recommend the use of buffy-coat-depleted RBC to prevent FNHTR in low-risk patients, while leucoreduction by filtration should be restricted to patients with the well-known indications[5].

In conclusion, ULR is a paradigm of the urgent need for authoritative, evidence-based practice guidelines defining common practices in all aspects of transfusion medicine including blood collection, component preparation, pre-transfusion testing, and testing for transfusion-transmitted diseases. Blood banks should be responsible for optimal blood safety, as determined by objective need, clinical results and cost efficacy. Finally, it must be stressed that blood safety is a matter of interplay between the cost-effective implementation of blood safety interventions and the appropriate usage of blood components.

The Authors declare no conflicts of interest.

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