Leucoreduction of blood components: clinical and molecular evidence

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Introduction

Transfusion of blood products is a life-saving intervention for millions of patients around the world. Significant strides have been made during the last 100 years in relation to sample collection, processing and storage technologies. One relatively recent innovation is the introduction of leucoreduction strategies which, through the use of filters, enable as much as a 3.5 to 4 log removal of white blood cells from a given blood component. As detailed in the most recent "National blood collection and utilization survey report" (World Health Organization, 2011)[1], leucoreduction practices have been shown to reduce the risk of febrile non-haemolytic reactions, transmission of cytomegalovirus infection and human leucocyte antigen (HLA) alloimmunisation, which may lead to platelet refractoriness. However, such technology has not been universally adopted by national blood services. For example, only 55.7% of total component units processed in the USA in 2011 (14,758,000), including paediatric aliquots, were leucoreduced by blood centres and hospitals collecting blood[1]. However, there was a 4% increase in this practice in the USA from 2008 to 2011, when ~85% of all whole blood units/red blood cell concentrates, and ~87% of apheresis platelet concentrates were leucocyte reduced either before or after storage[1]. Overall, the increased frequency of leucoreduction practices in the USA from 2008 to 2011 was mainly attributed to hospitals collecting blood (+26%), while the number of leucoreduced units produced by USA blood centres declined in the same time window by 15%[1].

A timely review of evidence-based literature

In the light of this information, it is evident that clear and universally accepted guidelines are still lacking, and new, informed guidelines should be discussed on the basis of cost-effectiveness considerations and evidence-based results. On this background, the timely review by Bianchi and colleagues from the Italian National Blood Centre addresses an extremely relevant issue in the field of transfusion medicine[2]. Results on evidence-based indications regarding the proven clinical efficacy of leucoreduction strategies from clinical studies are collected in the review and critically discussed by the authors.

Clear indications are provided in relation to the effectiveness and the desirability of leucoreduction strategies in platelet products to be transfused to high-risk patients, as a measure to prevent platelet alloimmune refractoriness and hypoproliferative thrombocytopenia[2].

The authors also comment on the reduced risk of cytomegalovirus transmission associated with the transfusion of leucoreduced units (risk reduced by 92.3%), even though more restrictive policies towards cytomegalovirus-seropositive donors may be more effective (risk reduced by 93.1%)[2].

Retrospective analysis of data collected after the introduction of leucoreduction strategies in comparison to existing data suggests that leucoreduction may reduce the risk of febrile non-haemolytic anaemia, a rare sequela of transfusion defined as the "rise in temperature greater than or equal to 1 °C that cannot be explained by the patients' clinical picture"[2].

Bianchi and colleagues then comment on the potential immunosuppressive effect of blood transfusions, encompassing the conflicting conclusions emerging from randomised clinical trials. In this context, the authors point out how clinical effects of leucoreduction technologies on recipients' "immunosuppression may be smaller than is detectable by trials"[2]. On the other hand, limited but promising evidence in animal models suggests that leucoreduction might be effective in preventing the transmission of variant Creutzfeld Jakob disease, although further studies are awaited.

Leucoreduction (as well as leucocyte inactivation and gamma irradiation) appears to be beneficial in decreasing the risk of transfusion-associated Graft-versus-Host disease, a transfusion-related complication that is triggered by the exposure to allogeneic donor leucocytes[2]. On the other hand, prevention of transfusion-related acute lung injury (TRALI) is mostly based on the "exclusion from clinical use of high-plasma volume blood components donated by multiparous and/or transfused donors, as well as donors involved in TRALI cases or with proven HLA or human neutrophil antigen antibodies"[2]. However, no evidence-based benefits have

been documented regarding the potential prevention of TRALI or transfusion-associated Graft-versus-Host disease in leucoreduced blood components. Finally, the authors comment on the controversies regarding the cost-effectiveness of leucoreduction strategies[2].

Laboratory evidence and "omics" technologies

Given the rarity of some of the adverse sequelae to transfusion therapy, most clinical trials have not been sufficiently powered to demonstrate some of the expected benefits associated with the implementation of leucoreduction strategies[2]. As a result, evidence-informed conclusions have been sometimes difficult to draw. Conversely, laboratory studies have widely documented a beneficial role of leucoreduction technologies in mitigating the rate and severity of the so-called "storage lesion"[3]. The storage lesion is a term that collectively refers to a wide series of morphological, mechanical and biochemical alterations targeting erythrocytes stored under blood bank conditions[3]. The storage lesion may potentially affect the safety and effectiveness of transfusion therapy[3].

Over the years, various studies have been performed by several groups in the field, mostly exploiting state-of-the-art analytical technologies referred to as "omics". Omics technologies are comprehensive analytical strategies, often adopting cutting-edge ultra-high performance liquid chromatography and mass spectrometry. These technologies are used to monitor specific classes of biomolecules, such as proteins (proteomics) or small molecule metabolites (metabolomics) over the duration of storage[3]. Results of omics studies by several groups, including but not limited to those of Hansen, Papassideri, Sparrow and Zolla, have independently and unanimously shown beneficial effects of leucoreduction of different blood components in mitigating the severity of the storage lesion (extensively reviewed by D'Alessandro *et al*.[3]). Benefits mostly relate to the slower accumulation of oxidative stress to proteins (e.g. non-reducible peroxiredoxin 2 dimers, carbonylation, protein fragmentation) and lipids, release of white blood cell-derived cytokines and vesicles[3]. On the other hand, Silliman's group has shown that leucoreduction does not entirely prevent the storage-dependent accumulation of bioactive lipids in erythrocyte concentrates, hydrophobic molecules that represent potential mediators of the second injury in the two-hit model of TRALI[4]. However, overall, beneficial effects are evident from a molecular standpoint, also given the appreciation of the potential impact of filtration efficacy on the supernatant levels of proteins and small molecule metabolites deriving from the residual white blood cells in ~>3log-filtered units[5].

Future evidence-based and laboratory studies will address the questions as to whether and to what extent the invaluable considerations on leucoreduction presented by Bianchi and colleagues in their review[2] will need to be readdressed upon the likely introduction of pathogen reduction technologies for blood products[6]. Although making blood products up to 1,000-fold safer, pathogen reduction approaches, which rely on the incubation of blood components with DNA intercalating agents prior to their photoactivation with ultraviolet light[6], may also target nucleated white blood cells. Additional studies may thus become necessary to disentangle the relative contribution to the storage lesion of pathogen inactivation and pre-inactivation leucoreduction, the latter representing a strategy to avoid the accumulation of white blood cell breakdown products in blood components from the very beginning of the storage period.

Disclosure of conflicts of interest

Although unrelated to the contents of the paper, AD declares that he is a member of Endura, LLC and consultant for New Health Sciences Inc.

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