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Review Article

The Effects of Chronic Inflammatory Disorders and Storage Lesions on Cytokine Levels in Blood Transfusion Products

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Abstract

Whole blood donated for transfusion is processed into four blood products, namely Red Cell Concentrates (RCCs), Fresh Frozen Plasma, Buffy Coats (BCs), and Platelet Concentrates which are obtained by further processing of BCs. These blood products are then given to vulnerable patient cohorts such as anaemic, cancer or post-operative patients requiring RCCs. However, these blood products may contain biomolecules such as inflammatory mediators that may cause adverse yet often overlooked effects in the recipient. Chronic inflammation is characteristic of numerous diseases such as cardiovascular diseases, cancer, type 2 diabetes, rheumatoid arthritis, inflammatory bowel disease, asthma and psoriasis. Such diseases elevate pro-inflammatory cytokines including Interleukin (IL)-1, IL-6 and Tumour Necrosis Factor (TNF)-alpha in the blood. Moreover, pro-inflammatory cytokines also accumulate in blood products during storage, mainly as a result of damaged leucocytes, and may cause Transfusion-Associated Adverse Reactions (TAARs) and transfusion-induced systemic inflammation. Although this is well-known, very little scientific research has investigated the clinical implications and actual adverse effects these abnormal cytokine levels in blood products from donors with underlying chronic inflammatory diseases have on vulnerable recipients, particularly critically-ill patients who are already prone to inflammation.

Keywords: Blood transfusion; Inflammation; Type 2 diabetes mellitus; Cytokines; Storage lesions

Abbreviations

BC: Buffy Coats; EDQM: European Directorate for the Quality of Medicines; IL: Interleukin; LR: Leucoreduced; FNHTRs: Febrile Non-Haemolytic Transfusion Reactions; QC: Quality Control; RCCs: Red Cell Concentrates; TAARs: Transfusion-associated adverse reactions; TRALI: Transfusion-related Acute Lung Injury; TRIM: Transfusion-Related Immunomodulation; TNF: Tumour necrosis factor; T2DM: Type 2 Diabetes Mellitus

Introduction

Modern transfusion medicine revolves around effectively targeting the specific needs of the recipient, optimising the use of blood products and ensuring appropriate storage conditions to extend their shelf lives. To achieve this the donated Whole Blood needs to be processed. This processing yields three distinct blood components: Red Cell Concentrates (RCCs), Fresh Frozen Plasma and the Buffy Coat (BC). An additional processing of the BCs will produce a further blood component which is the Platelet Concentrate. The transfusion of blood and blood products has been utilised as a life-saving therapeutic procedure since the early 20th century [1]. Despite this, transfusion is known to bear inherent risks, which have resulted in the adoption of restrictive clinical practice guidelines as opposed to the more liberal ones previously used. This was done with the intention of optimising the use of these oftentimes costly and scarce blood products in a way which enhances patient outcomes, minimises unnecessary risks and reduces costs [2].

The transfusion of red cells has become a commonly used therapeutic procedure, with approximately 85 million units transfused globally each year [3]. Anaemic, cancer and post-operative patients are among the most common patient populations that benefit from RCCs. Despite this, red cell transfusions pose several risks including febrile or haemolytic reactions, allergic reactions, infectious complications, transfusion-associated circulatory overload and Transfusion-Related Acute Lung Injury (TRALI) [4]. In light of this, blood transfusion establishments carry the enormous responsibility of safeguarding the health of both the blood donors and recipients whilst maintaining an adequate supply of safe and effective blood products. This is achieved through the implementation of a national system for donor selection involving standardised questionnaires, interviews and medical examinations [5]. Core questions revolve around the donor's medical, travel and family history and high-risk behaviours so as to ascertain the prospective donor is in good health and does not pose a risk of transfusion-transmissible infections. Moreover, the donor should be between the ages of 17 and 65, have a minimum weight of 50kg, a haemoglobin and blood pressure level in the normal range and should not be febrile [6]. In addition, the process of Quality Control (QC) analysis of blood products based on a number of QC parameters, which are carefully selected by the appropriate control authority, aims to verify the quality, safety, and efficacy of blood products [5].

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Inflammatory Diseases

Inflammation is a complex defence mechanism mounted by the host's immune system in response to tissue injury or infection. It involves the initiation of a chemical signalling cascade, with the aim of promoting the healing process [7]. Historically, inflammation was characterised by redness, heat, swelling and pain but is nowadays recognised to also be present more subtly [8]. Although inflammation is typically regarded as an essential and protective response, this only holds true when it is self-limiting. Chronic diseases such as cardiovascular diseases, cancer, diabetes and arthritis result partly from the failure of the mechanism of body to resolve inflammation *via* inflammatory mediators [7].

Inflammatory Markers

Cytokines are small soluble immunomodulatory proteins involved in the regulation of inflammation that are secreted mainly by immune cells in response to pathogens or other stress stimuli [7]. The major hallmarks of cytokines include their redundancy, in that different cytokines may produce similar effects as well as their pleiotropic nature, meaning their effects may vary depending on the targeted cell type [9]. Moreover, cytokines are observed to act either synergistically or antagonistically [10].

Cytokines are described as being pro-inflammatory or anti-inflammatory, both of which accumulate in blood products during storage mainly as a result of damaged leucocytes [11]. The accumulation of pro-inflammatory cytokines, such as Interleukin (IL)-1, IL-6 and Tumour Necrosis Factor (TNF)-alpha, is regarded as one of the major causative factors For Transfusion-Associated Adverse Reactions (TAARs) [12], particularly Febrile Non-Haemolytic Transfusion Reactions (FNHTRs) and Transfusion-Related Immunomodulation (TRIM) [13]. In addition, the transfusion of blood products containing cytokines has been associated with transfusion-induced systemic inflammation in patients with pre-activated endothelial cells [14]. Conversely, anti-inflammatory cytokines, especially IL-10, aid in alleviating inflammation and promoting healing by suppressing pro-inflammatory cytokine genes [15]. The uncontrolled production of pro-inflammatory cytokines, especially TNF-alpha, IL-1 and IL-6, has been implicated in the pathogenesis of a number of chronic inflammatory diseases [16]. The most widely studied inflammatory diseases associated with this phenomenon include rheumatoid arthritis and inflammatory bowel disease. Other related inflammatory disorders commonly found in Europe include asthma and psoriasis.

Type 2 Diabetes Mellitus

Diabetes is one of the fastest growing non-communicable diseases, often regarded as a global epidemic [17,18]. The estimated global prevalence of diabetes in 2019 according to the International Diabetes Federation was 463 million [18] and is projected to increase to 693 million by 2045 [19], with Type 2 Diabetes Mellitus (T2DM) accounting for approximately 90% of all cases. This places enormous importance on preventive measures and early detection to minimise the substantial burdens associated with T2DM and its complications. T2DM has been increasingly recognised as an inflammatory disease due to its underlying inflammatory pathogenesis. It is considered a chronic metabolic disorder which is characterised by hyperglycaemia as a consequence of insulin resistance, reduced insulin secretion and subsequent failure of the pancreatic beta-cells [20]. The insulin resistance stage refers to the inability of the cells, such as those in the liver and muscles, to respond adequately to the action of insulin, thereby resulting in a compensatory increase in the production of insulin to control increasing glucose levels. Eventually, the pancreatic beta-cells become dysfunctional due to the sustained increased demands, leading to insufficient production of insulin and chronic hyperglycaemia [21]. Although more common in adults, T2DM is increasingly being diagnosed in children and adolescents, in parallel with the increasing incidence of childhood obesity, which is one of the strongest T2DM risk factors. This stems from an increased shift towards unhealthy eating habits and sedentary lifestyles. It has been found that approximately 60% of T2DM patients are obese [22]. An area of concern is that approximately half of T2DM individuals remain undiagnosed despite the readily available tests [19]. In fact, about a fourth of newly diagnosed individuals already have microvascular complications, indicating that they would have had the disease for at least 4-7 years prior [20,23]. The gradual development of the mild and oftentimes overlooked T2DM symptoms including polydipsia, polyuria, fatigue, blurred vision and slow wound healing, account for this [24].

Currently, blood donors with T2DM who do not require insulin therapy are allowed to donate blood [6]. In addition, a systematic literature review, although relying on a paucity of relevant studies, indicates that the act of blood donation is not associated with an increased risk of adverse reactions in T2DM blood donors [25]. Despite this, the current state of knowledge with regards to the abnormal cytokine levels associated with this inflammatory disease [26] leads one to question the clinical implications of the transfusion of blood products from such donors. This is especially true in the case of critically-ill patients in whom excessive inflammation and immunomodulation related to cytokine levels are associated with negative outcomes [11].

Red Cell Concentrate Storage Lesions

Storage lesions are defined as the accumulation of certain physicochemical changes related to increased storage durations of blood units in unnatural *in vitro* conditions [12]. Despite major efforts to maximise the shelf life of blood products, while maintaining their optimal effectiveness and safety, these degradative changes are unavoidable and often irreversible [12]. Root causes behind red cell storage lesions have been attributed to oxidative stress in the absence of *in vivo* physiological protective mechanisms, as well as the depletion and concurrent accumulation of certain metabolites such as lactate in a closed system, leading to an acidic environment and impaired cellular function [27]. Storage lesion-related changes include, amongst others, altered oxygen affinity, RBC morphological changes, impaired RBC stability, and depletion of adenosine triphosphate and 2, 3-diphosphoglycerate [12]. A number of these progressive changes have been associated with TRIM and an increased risk of TAARs [28]. In particular, the release of nitric oxide-scavenging free haemoglobin and microparticles have been implicated in the pathogenesis of TRALI [29]. Moreover, the production and accumulation of cytokines during storage as observed by Chukwu et al., [13], amongst others, is regarded as a major causative factor of TAARs.

Elevated levels of pro-inflammatory cytokines have been

invariably associated with both TRALI and FNHTRs [12]. The accumulation of cytokines is suggested to result from their release by damaged leucocytes in stored blood products [13]. However, Karsten et al., [30] detected 46 cytokines in RBC lysates with a median concentration 12 times higher than in the plasma, while macrophage migration inhibitory factor was detected in abundance in a separate study [31]. This indicates that RBCs play an unexplored role in cytokine signalling and TRIM. This is further supported by the notion that TRIM is observed even following leucoreduction. Nevertheless, residual leucocytes in stored blood products are still recognised to have unfavourable immunomodulatory effects. In fact, the use of Leucoreduced (LR) blood units, as opposed to non-LR units - which have nowadays been largely discontinued - has been seen to improve clinical outcomes, reduce nosocomial infections and reduce systemic inflammation following cardiac surgeries [11].

Conclusion

TAAR is the recipient's immunomodulatory response to a transfusion that may range from mild to severe. To mitigate such an outcome, stringent regulations have been imposed, ensuring that the blood is both safe and of good quality. The identification of the inflammatory basis of T2DM was a landmark in clinical research. This has allowed a better understanding of the development of the disease and has opened up further research centred around new anti-inflammatory therapeutic approaches. Moreover, the associated elevated cytokine levels seen in T2DM individuals [32] has led to the idea that RCCs from borderline or undiagnosed diabetic blood donors would have abnormal cytokine levels in comparison with non-diabetic donors. Similarly, studies have identified storage lesions which contribute to abnormal levels of pro-inflammatory cytokines as being implicated in a number of adverse transfusion reactions, including FNHTRs and TRIM [13]. Increasingly common diseases such as obesity and T2DM are associated with abnormal cytokine levels and oxidative stress, similar to that seen in storage lesions [33]. One might question the implications for the quality and safety of blood products from such donors. Currently, inflammatory parameters such as cytokine level determination and glucose testing are lacking during the donor selection process. Despite this, it is interesting to note that glucose urine testing was a requirement at the pre-blood donation stage but over the years this was determined to be unnecessary by the European Directorate for the Quality of Medicines (EDQM) and thus discontinued. In addition, as per the EDQM guidelines [5], donors with T2DM are allowed to donate blood irrespective of what pharmacological agents they are using, so long as they do not require treatment with insulin or injectable medications and do not suffer from diabetes-related complications. Nonetheless, this specific phenomenon has only been superficially explored in the literature as of yet. Hence, the clinical effects of transfusing blood products, especially RCCs, from donors with T2DM or other inflammatory conditions to critically-ill recipients, particularly cancer and paediatric patients in whom immune suppression and excess inflammation are strongly associated with adverse outcomes [11] would be an interesting area for further research. To date, although the literature is well versed with studies investigating storage lesions and the clinical aspects of T2DM, the clinical implications of combining the two remain largely unknown. An interesting approach would be screening such donors for a selection of inflammatory markers and testing the recipient before and after transfusion to determine if such blood would indeed have any adverse effects. However, implementing such a plan would require the coordination and management of several interdisciplinary professionals.

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