Disponible en ligne sur ScienceDirect www.sciencedirect.com

Elsevier Masson France EM|consulte www.em-consulte.com

TRANSFUSION CLINIQUE ET BIOLOGIQUE

Transfusion Clinique et Biologique 24 (2017) 87–91

Research perspective

Determination of predictors of severity for recipient adverse reactions during platelet product transfusions

Détermination des prédicteurs de sévérité des effets indésirables receveurs au cours des transfusions de produits plaquettaires

C. Sut [a,b], S. Tariket [a,b], F. Cognasse [a,b], O. Garraud [a,c,*]

[a] *Université de Lyon, GIMAP-EA3064, 42023 Saint-Étienne, France*
[b] *Établissement français du sang Rhône-Alpes-Auvergne, 42023 Saint-Étienne, France*
[c] *Institut national de la transfusion sanguine, 75015 Paris, France*

Available online 4 May 2017

Abstract

The introduction of allogeneic cells is not a natural process, even if the transfusion is therapeutic and — when no alternative exists, as is often the case — essential. Transfusion of cellular products creates some level of danger sensed by recipients. Danger may manifest itself clinically or biologically, in which case we are dealing with recipient adverse reactions. Platelet concentrate transfusion in particular may be responsible for notable adverse reactions. Some appear to be inevitable, while others are tied to recipient factors: either health or genetic characteristics. The authors' research is specifically focused on platelet storage lesion and stress factors, and the means of controlling them to ensure greater recipient tolerance.

Keywords: Transfusion; Platelets; Inflammation; Adverse reactions; Biological response modifier; Endothelial cells

Résumé

L'apport de cellules homologues (allogéniques) n'est pas physiologique quand bien même la transfusion est thérapeutique et essentielle en ce sens qu'il n'y a fréquemment pas d'alternative. La transfusion de produits cellulaires créée une situation de danger chez le receveur. Ces situations de danger peuvent occasionnellement s'exprimer cliniquement ou biologiquement : on parle alors d'effet indésirable receveur (EIR). La transfusion de concentrés de plaquettes en particulier peut être responsable d'effets indésirables notables, dont une partie semble évitable et une partie est liée à des facteurs du receveur, soit de par son état clinique, soit de par ses propres caractéristiques génétiques. Ce travail se focalise plus particulièrement sur les facteurs de stress ou lésions de stockage des produits plaquettaires et les moyens de les contrôler pour une meilleure tolérance par les receveurs.

Mots clés : Transfusion ; Plaquettes ; Inflammation ; Effets indésirables receveurs ; Modificateurs du comportement biologique ; Cellules endothéliales

1. Introduction

In France, near 3,200,000 labile blood product (LBPs) transfusions take place each year. There are three kinds of LBPs: red cell concentrates (RCCs), platelet concentrates (PCs), and plasma for various therapeutic purposes. Most transfused LBPs are RCCs (79%), plasma comes in second (11%), and PCs follow

* Corresponding author at: Institut national de la transfusion sanguine, 6, rue Alexandre-Cabanel, 75739 Paris cedex 15, France.
E-mail address: ogarraud@ints.fr (O. Garraud).

http://dx.doi.org/10.1016/j.tracli.2017.04.002
1246-7820/

close behind (10%) [1]. All LBPs are derived from voluntary, ethically obtained, unpaid whole blood or apheresis donations made by healthy donors. To ensure safe, optimal transfusion, strict rules apply to the collection, preparation, storage, and prescription of blood products.

During or following a blood transfusion — especially a platelet transfusion — the recipient may experience an adverse reaction (AR). The severity of ARs varies: they are most often benign, sometimes serious, and rarely lethal. Every LBP transfusion is affected by donor phenotypic characteristics, which exert effects during the process of preparing and storing the products; by recipient health characteristics; or by both. These parameters are the three variables of the transfusion triangle: donor–product–recipient. During preparation and storage of the PCs, accumulation of cytokines and chemokines may trigger an inflammatory reaction in the recipient [2].

Among the main cytokines/chemokines called Biological Response Modifiers (BRMs) are immunomodulatory molecules, many of which are pro-inflammatory and may be involved in several tissue pathologies [3]. These BRMs act as ligands for receptors on endothelial cells and most kinds of leucocytes that are in circulation or that adhere to the endothelium.

2. Platelet concentrates

Platelets play a specialized role in the haemostatic response that stops bleeding after damage to a blood vessel [4]. They also participate in immune responses by acting as modulators and mediators of the inflammatory response [5]. Platelets express receptors that bind ligands involved in various stages of innate or adaptive immune response [6], and they also produce soluble inflammatory factors [7]. PCs may be derived from whole blood or plateletpheresis donations. Each type is used to prepare a distinct product. Pooled whole-blood-derived platelet concentrates (PPCs) are obtained from the buffy coat layers of several whole-blood donations (presently limited to five in France). Apheresis platelet concentrates (APCs) are obtained using an apheresis machine that isolates the platelets from the blood of a single donor. In France, PPCs and APCs are stored in a mixture of 35% donor plasma and 65% additive solution. PCs are stored for five days or less at $22 \pm 2\,^{\circ}C$. They are constantly gently agitated to prevent platelet aggregation. All LBPs must undergo leucocyte reduction: after this process, there must be $< 10^6$ leucocytes per unit of product. LBPs are screened in compliance with EU and French standards, and they are labelled per regulations according to blood group.

3. Recipient adverse reactions

In spite of the strict precautions taken for LBP preparation and storage, there may be complications — i.e. ARs — following a blood transfusion. The principal ARs reported are alloimmunization, inflammation, excess blood volume, and infection. Though viral and parasitic infections are now rare, professionals are particularly apprehensive about bacterial infections — especially those associated with PCs. Inflammatory incidents include febrile non-haemolytic transfusion reactions (FNHTRs), allergic reactions, cardiovascular reactions (e.g. hypotension), and transfusion-related acute lung injury (TRALI) [8]. Though PCs account for only 10% of all LBP transfusions, they are responsible for 40% of all ARs [9]. Interactions between platelets, immune cells, and endothelial cells play a major role in the occurrence of an AR.

4. Platelets and inflammation

PCs are therapeutic products subject to regulatory and safety requirements. However, they contain immunomodulatory BRMs that may trigger ARs.

4.1. BRMs associated with platelets

Platelets contain soluble factors responsible for inflammatory or allergic reactions. It has been shown that during platelet transfusion, BRMs can induce immune responses [10] or post-transfusion reactions [11], affect haemostasis [12], or cause inflammation in recipients [13]. These substances — categorized as cytokines/chemokines — have immunomodulatory effects, and their secretions can vary depending on how platelets are activated. Which contents platelets release is a function of the kind of stimulus [14]. Although platelets are anucleate, they do contain α-granules, δ-granules, T granules, and lysosomes, which enclose molecules of many types involved in inflammatory and allergic reactions [15]. Some cytokines/chemokines and related molecules produced by platelets may play a part in the advent of an AR.

4.2. Identification of factors promoting BRM secretion

Concentration of BRMs in PCs is partly determined by the preparation and storage processes applied and by the age of the platelets. Platelets are subject to stress damage during collection, processing, and storage [16]. The kinds of stress to which platelets are subjected vary by PC preparation technique, and studies have shown that these techniques differ in their effects on pro-inflammatory reactions [17]. Here, we are interested in how preparation and storage affect platelet inflammatory properties, in order to optimize PC quality. Our team demonstrated that immunomodulatory factors are found in PC supernatants secreted during preparation and storage [2]. BRMs present during preparation of non-leucoreduced PCs are of three origins: from leucocytes, plasma, or platelets. PC leucocyte reduction considerably lowered the concentration of these factors, including TNF-, IL-6, and IL-8 [15], and consequently the incidence of ARs involving leucocyte cytokines. However, some cytokines are released by the platelets themselves during PC storage. These include sCD40L, PDGF-AA, RANTES, IL-6, and TGF-β [2]. In general, BRM production increases with length of PC storage. This may be linked to AR incidence, which has been observed to increase as storage time lengthens. To lessen this incidence, PCs should be transfused as soon as possible. Our team showed that the concentration of PC BRMs — sCD40L in particular — increases significantly starting on the third day of PC storage. These observations suggest that storage lesions have a major