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Review

Microparticle content of platelet concentrates is predicted by donor microparticles and is altered by production methods and stress

Elisabeth Maurer-Spurej [a,b,c,*], Rune Larsen [d], Audrey Labrie [b], Andrew Heaton [e], Kate Chipperfield [f]

[a] Centre for Blood Research, Canadian Blood Services, Vancouver, BC, Canada
[b] LightIntegra Technology Inc., Vancouver, BC, Canada
[c] Department of Pathology and Laboratory Medicine, University of British Columbia, Vancouver, BC, Canada
[d] Department of Clinical Immunology, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark
[e] HeatonDx Consulting, San Francisco, CA, USA
[f] Hematopathology, British Columbia Children's Hospital, Vancouver, Canada

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ABSTRACT

In circulation, shedding of microparticles from a variety of viable cells can be triggered by pathological activation of inflammatory processes, by activation of coagulation or complement systems, or by physical stress. Elevated microparticle content (MPC) in donor blood might therefore indicate a clinical condition of the donor which, upon transfusion, might affect the recipient. In blood products, elevated MPC might also represent product stress. Surprisingly, the MPC in blood collected from normal blood donors is highly variable, which raises the question whether donor microparticles are present in-vivo and transfer into the final blood component, and how production methods and post-production processing might affect the MPC. We measured MPC using ThromboLUX in (a) platelet-rich plasma (PRP) of 54 apheresis donors and the corresponding apheresis products, (b) 651 apheresis and 646 pooled platelet concentrates (PCs) with plasma and 414 apheresis PCs in platelet additive solution (PAS), and (c) apheresis PCs before and after transportation, gamma irradiation, and pathogen inactivation (N = 8, 7, and 12 respectively). ThromboLUX-measured MPC in donor PRP and their corresponding apheresis PC samples were highly correlated ($r = 0.82$, $P = .001$). The average MPC in pooled PC was slightly lower than that in apheresis PC and substantially lower in apheresis PC stored with PAS rather than plasma. Mirasol Pathogen Reduction treatment significantly increased MPC with age. Thus, MPC measured in donor samples might be a useful predictor of product stability, especially if post-production processes are necessary.

Contents

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* Corresponding author. Centre for Blood Research, University of British Columbia, 2350 Health Sciences Mall, Vancouver, BC V6T 1Z3, Canada. Fax: +1 604 628 7880.
E-mail address: emaurer@mail.ubc.ca (E. Maurer-Spurej).

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1. Introduction

Microparticles are an important factor in transfusion medicine [1–3]. These small vesicles found in blood plasma play complex and dynamic physiological roles as mediators of far-reaching intercellular communication by expressing a variety of membrane-associated proteins and by transferring receptors, growth factors, and microRNA [1–4]. Microparticles can be markers of inflammation [4] and hypercoagulation [3]. Microparticles are continuously released from red blood cells, white blood cells, endothelial cells, and platelets in response to epinephrine, ADP, thrombin, collagen, and Ca^{2+} ionophore, or as a result of the extracorporeal storage [1]. Seventy to ninety percent of microparticles are derived from platelets [5,6]. Platelets, in addition to responding to agonists, generate microparticles in response to complement activation, shear forces, senescence, and cytoskeletal abnormalities [2]. Increased concentration or altered characteristics of plasma microparticles in vivo are associated with hypertension [7], cardiovascular disease [8], recurrent miscarriage [9], transfusion-related acute lung injury [10], bacterial endotoxin [11], hypercoagulability in type 2 diabetes [12], Crohn's disease [13], sepsis [14,15], and auto-immune diseases such as rheumatoid arthritis, psoriasis and asthma [16–18], and melanoma [19]. In addition, the proportional increase of microparticle content (MPC) relative to platelet concentration during storage of platelet concentrate (PC) can be attributed to different methods of separation or varying processing conditions [20].

In blood products, elevated MPC might therefore indicate an undesirable condition in the donor that could affect the recipient after product transfusion. In fresh platelet products, MPC may indicate the level of stress that platelets were exposed to in the donor or during product separation [1,21]. Consequently, high MPC in the transfused platelet product could, for example, reduce platelet recovery by a direct effect on the recipient's immune system [1] or because the stress that generated the microparticles in the donor, or during product separation, marks the platelets for removal from circulation [22,23]. In addition, storage lesion also generates microparticles with aging of the platelet product [1,3]. Microparticles may participate in endothelial and macrophage activation, which in turn may shorten the platelet life span [24].

Surprisingly, the MPC in blood from normal healthy transfusion donors is highly variable and affected by diet [25,26] and exercise [27]. This observed variation raises the question of the extent to which donor microparticles transfer into the donated product and how production methods and post-production processing might affect the MPC. One immunocytochemistry study describes the carryover of donor microparticles into the apheresis product, where the microparticles appear to be mainly harvested from the donor [28]. Thus, MPC measured in donor samples might be a useful predictor of blood product MPC and therefore product stability.

Several technologies have been used and described in the literature for the measurement of microparticles in blood and other body fluids [1,21,24,29], including established methods such as flow cytometry and dynamic light scattering [30]. The measurement principle of the ThromboLUX microparticle assay is dynamic light scattering, which has long been used in the pharmaceutical industry for quality control of liposomal drugs, which are in the size range of microparticles. Dynamic light scattering is ideally suited for routine screening of particle content based on size but not for functional characterization of these particles. The special DLS setup in ThromboLUX also allows microparticle enumeration to be performed in native platelet-rich plasma and platelet concentrate samples, i.e., without removal of platelets, which is essential for routine screening. The ThromboLUX microparticle assay is validated as a measure of MPC in pooled PC because it correlates highly with measures of microparticle concentration obtained by flow cytometry [31].

We hypothesized that the origin of microparticles in PCs is the donor, and that post-production processing – such as substitution of plasma with platelet additive solution (PAS), transport, irradiation, or pathogen inactivation – can decrease or increase the MPC. Accordingly, we investigated the relationship between the MPC of each donor's platelet-rich plasma (PRP) sample before apheresis and the MPC in the donor's corresponding apheresis PC. We chose apheresis