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Full Length Article

Platelet storage lesion in interim platelet unit concentrates: A comparison with buffy-coat and apheresis concentrates

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ABSTRACT

Platelet storage lesion is characterized by morphological changes and impaired platelet function. The collection method and storage medium may influence the magnitude of the storage lesion. The aim of this study was to compare the newly introduced interim platelet unit (IPU) platelet concentrates (PCs) (additive solution SSP+, 40% residual plasma content) with the more established buffy-coat PCs (SSP, 20% residual plasma content) and apheresis PCs (autologous plasma) in terms of platelet storage lesions. Thirty PCs (n = 10 for each type) were assessed by measuring metabolic parameters (lactate, glucose, and pH), platelet activation markers, and *in vitro* platelet aggregability on days 1, 4, and 7 after donation. The expression of platelet activation markers CD62p (P-selectin), CD63 (LAMP-3), and phosphatidylserine was measured using flow cytometry and *in vitro* aggregability was measured with multiple electrode aggregometry. Higher platelet activation and lower *in vitro* aggregability was observed in IPU than in buffy-coat PCs on day 1 after donation. In contrast, metabolic parameters, expression of platelet activation markers, and *in vitro* aggregability were better maintained in IPU than in buffy-coat PCs at the end of the storage period. Compared to apheresis PCs, IPU PCs had higher expression of activation markers and lower *in vitro* aggregability throughout storage. In conclusion, the results indicate that there are significant differences in platelet storage lesions between IPU, buffy-coat, and apheresis PCs. The quality of IPU PCs appears to be at least comparable to buffy-coat preparations. Further studies are required to distinguish the effect of the preparation methods from storage conditions.

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1. Introduction

Platelet function disorders and thrombocytopenia are often treated with transfusion of platelet concentrates (PCs). In addition, patients with ongoing spontaneous, perioperative, or traumatic bleeding may receive platelet transfusions to enhance hemostasis. The PCs are stored in a platelet incubator until use, or for a maximum of 5–7 days. However, long PC storage time has been shown to have a negative effect on platelet quality, a process termed platelet storage lesion [1,2].

PCs are prepared by different methods. The main differences between the three types of PCs in this study include the collection and preparation method, the storage medium, and plasma content. Interim platelet unit (IPU) PCs are a newly introduced type of PC that are prepared from whole blood donations and only require one platform for centrifugation, separation of components, and pooling into a single unit [3]. IPUs from multiple donors are pooled together in platelet additive solution (PAS) to produce one platelet unit. Other more established types of PCs include buffy-coat PCs and apheresis PCs. Pooled buffy-coat PCs are also prepared from whole blood donations, and buffy coats of multiple donors are pooled together in PAS to produce one platelet unit. Apheresis PCs are derived from a single platelet donor using an apheresis device, and the platelets are stored in autologous plasma or in a mix of plasma and PAS.

The aim of this study was to compare the new IPU PCs with the currently used buffy-coat PCs and apheresis PCs in terms of platelet storage lesion markers including metabolic parameters, platelet activation and *in vitro* platelet aggregability.

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2. Materials and methods

2.1. Platelet concentrates

In order to conduct a real life comparison, reflecting the actual product given to the patients, IPU, buffy-coat and apheresis PCs (n = 10 each) were prepared according to local guidelines, i.e. plasma content and storage medium differed between the PCs. The platelets were derived from blood donors at Sahlgrenska University Hospital. All donors fulfilled the donation criteria and signed the health questionnaire. Preparation of the PCs was done by the regional blood bank in accordance with European guidelines [4]. Leukocyte reduction was performed ($<1 \times 10^6$ leukocytes per unit) and the PCs were gamma-irradiated (25 Gray). The PCs were placed in a platelet incubator (Helmer Agitator; Fenwal Europe, Mont Saint Guibert, Belgium) at 22 °C with horizontal agitation until use.

2.1.1. Interim platelet unit concentrates

IPU PCs were prepared from whole blood donations. Whole blood units were collected in blood collection bags (450 mL) (Reveos; Terumo BCT Europe, Zaventem, Belgium) containing the anticoagulant citrate phosphate dextrose (CPD, 63 mL). Whole blood was separated on the Reveos system into its components within 2–8 h after donation. The processing program 3C was used according to the settings provided by the manufacturer. This gives three components: one unit of red cells, one unit of plasma, and one interim platelet unit (IPU). Also, a waste unit or leukopack containing most white blood cells was obtained. The IPU consisted of platelets in approximately 30 mL of autologous plasma, and it was placed in a platelet incubator with horizontal agitation overnight to dissolve potential platelet aggregates. Based on the platelet count provided by the Reveos system, four IPUs were pooled together with PAS (SSP+; Terumo BCT Europe) to a target count of approximately 250×10^9/unit. The final IPU PC was leukoreduced by the in-line filter. The residual plasma content of the IPU PCs was approximately 40%.

2.1.2. Buffy-coat platelet concentrates

Buffy-coat PCs were prepared from whole blood donations. To collect the whole blood, bottom-and-top bags (450 mL) (MacoPharma Nordic AB, Helsingborg, Sweden) were used with 63 mL CPD. In order to obtain the buffy coats, the whole blood units were centrifuged ($4880 \times g$ for 11 min at 23 °C) and the blood components were separated using a blood expander platform (Macopress Smart; MacoPharma Nordic AB). The buffy coat was placed in a platelet incubator with horizontal agitation overnight. Four buffy coats were then combined to give one pooled unit in PAS (SSP; MacoPharma Nordic AB). To remove the remaining red blood cells, the pooled unit was processed in an automated blood component processing device (TACSI; Terumo BCT Europe). The residual plasma content of the buffy-coat PCs was approximately 20%.

2.1.3. Apheresis platelet concentrates

Apheresis PCs were collected using standard protocols (Trima Accel; Terumo BCT Europe). The minimum required donor platelet count was 230×10^9/L before donation, while the target concentration was $1{,}600 \times 10^9$/L and the ratio of whole blood to citrate was 10:1. The platelets were collected and stored in autologous plasma. After collection, the apheresis PCs were allowed to rest without agitation for 2 hours before further handling.

2.2. Study design

Aseptic sampling from the PCs was conducted using a sampling bag (MacoPharma; Mouvaux, France) on days 1, 4, and 7 after donation. Samples for lactate, glucose, and pH measurements were collected from the sampling bag using a syringe containing lithium heparin (Smiths Medical ASD Inc.; Keene, NH, USA). For platelet concentration, activation, and aggregation analysis, samples were placed in plastic tubes without additives.

2.3. Analyses

The platelet concentration was analyzed using automated cell counters (Cell-Dyn Sapphire; Abbott Diagnostics Division, Santa Clara, USA; or ABX Micros 80; Horiba, Irvine, CA, USA). Levels of lactate, glucose, and pH were measured at 22 °C using an ABL800 blood gas analyzer (Radiometer, Copenhagen, Denmark). Lactate production rates and glucose consumption rates on days 4 and 7 were calculated using values from day 1 as reference points. Platelet activation was evaluated by measuring the expression of the platelet activation markers CD62p (P-selectin), CD63 (LAMP-3), and phosphatidylserine (PS) using flow cytometry. For analysis of the platelet granule proteins CD62p and CD63, 30 μL of PC was fixed with 1% paraformaldehyde, washed with phosphate-buffered saline (PBS; 140 mM NaCl and 10 mM Na_3PO_4, pH 7.4) and then resuspended in PBS containing 2% fetal calf serum. Next, the monoclonal antibody CD61-FITC (platelet surface marker; GPIIIa) (BD Biosciences, San José, CA, USA) and either CD62p-PE, CD63-PE, or immunoglobulin G1-PE-FITC (IgG1-PE-FITC) (isotype control) (BD Biosciences) were added and incubated for 15 min. The isotype control was used to set the quadrant markers. Flow cytometry was performed within 30 min. For evaluation of PS exposure, 100 μL of PC was washed twice in PBS and diluted in 1 × Annexin V binding buffer (BD Biosciences). The monoclonal antibody CD61-FITC (platelet surface marker) and either IgG1-PE-FITC (isotype control) or Annexin V-PE (BD Biosciences) were added and incubated for 15 min. Flow cytometry was performed within an hour. All the samples were measured with a FACSCalibur flow cytometer (BD Biosciences). In total, 10,000 platelet events were acquired and analyzed using the software CellQuest Pro (BD Biosciences).

Multiple electrode aggregometry (Multiplate; Roche Diagnostics, Basel, Switzerland) was used to evaluate agonist-induced platelet aggregation in the PCs as previously described [1]. With this method, different agonists are used to induce platelet aggregation and the change in impedance between two electrodes in a test cell is measured. Each test cell contains two sets of electrode pairs. The impedance increases as aggregation occurs, and the results are presented as aggregation curves. The area under the curve (AUC) can be used to quantify aggregation. Briefly, 150 μL of PC was added to 450 μL PBS in each test cell for the apheresis PCs. For the IPU and buffy-coat PCs, 150 μL of the PBS was replaced with 150 μL of allogeneic plasma of blood group AB. The agonists used in this study were adenosine diphosphate (ADP), arachidonic acid (AA), collagen (COL), and thrombin receptor-activating peptide-6 (TRAP)-6 (Roche Diagnostics). The ADP test (6.5 μM ADP) measures $P2Y_{12}$ receptor-dependent platelet aggregation while the ASPI test reflects cyclooxygenase-dependent aggregation with arachidonic acid (AA; 0.5 mM) as an agonist. In the COL test, collagen (3.2 mg/L) is used as an agonist to study cyclooxygenase-dependent aggregation while the TRAP test uses thrombin receptor-activating peptide (TRAP)-6 (32 μM) to study PAR-1 receptor-dependent aggregation. The results were plotted as graphs in which the AUC, expressed in aggregation units, was used as a measure of the platelet aggregability.

2.4. Statistics

Data given in tables are median (25th percentile–75th percentile). Comparisons between IPU PCs and buffy-coat PCs, and between IPU PCs and apheresis PCs, were conducted with the Mann-Whitney U-test at each time point. No comparisons were

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