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Original article

A comparison of two protocols for optimal red blood cell depletion using Sepax-2 device for ABO-major incompatible transplantation in adults

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ABSTRACT

Purpose of the study: In ABO-incompatible bone marrow transplantation, an efficient depletion of red blood cells (RBC) within the graft is mandatory to avoid adverse events in transplanted patients. Using non therapeutic products, we evaluated the substitution of the standard density gradient-based separation (DGBS) over Ficoll-Paque with the use of an automated procedure intended for buffy coat only (SmartRedux software) introducing modifications within the settings to achieve a drastic reduction of the initial volume of the product. Both methods were conducted on the Sepax-2 device.
Samples and methods: RBC depletion rates and CD34+ cells recoveries from eight procedures with SmartRedux software using "in-house" settings (method A) were compared to those obtained from four procedures using NeatCell software, an automated DGBS over Ficoll-Paque (method B).
Results: Median erythrocyte depletion of 95,4% (92,7%–99,0%) and 99,8% (99,0%–99,9%) were observed using methods A and B, respectively. Median residual RBC volumes in the final product were 19 mL (4,4 mL–31,2 mL) and 0,7 mL (0,4 mL–4,7 mL), respectively ($p = 0{,}014$). CD34+ cells recoveries of 90,9% (62,7%–102,1%) and 78,4% (64,1%–86,2%) were achieved for methods A and B. Median platelet depletion was 16,6% (10%–42,7%) and 89,8% (88,5%-92,4%) using methods A and B, respectively ($p = 0{,}004$). Processing duration was shorter using method A (168 ± 29 min) than method B (295 ± 21 min) ($p = 0{,}004$).
Conclusion: Both methods achieved satisfactory erythrocyte depletion and CD34+ recovery. The use of Sepax-2 device in association with SmartRedux software could be extended to efficiently deplete RBC from large-volume BM in a raw instead of DGBS.

Introduction

In hematopoietic stem cell transplantation, the critical factor predicting successful engraftment and clinical outcome is the high degree of donor-recipient match in class I and II human leukocyte antigens (HLA). As HLA and ABO antigens are encoded by different genes, greater than 50% of unrelated donors and 30% of related donors demonstrate some degree of ABO incompatibility (ABOi) in bone marrow transplantation (BMT). ABOi is classified in one of three ways: major, minor or bidirectional (major and minor). In major ABOi BMT, complications are immediate acute hemolysis of incompatible red blood cells (RBC) usually spanning from 25 to 35% of the total volume of the graft, delayed engraftment and pure red cell aplasia (PRCA) [1]. Complications from acute hemolysis can be mitigated by the preemptive manipulation of the graft to remove RBC within the graft. Although neither safe criteria for a safe RBC maximum volume has been published, most institutions have established a upper limit for RBC between 20 and 30 mL or 0,2 to 0,4 mL/kg in pediatric transplantation [1,2]. Various methods have been used for RBC depletion such as RBC sedimentation using Hydroxyethyl starch (HES) sedimentation or density gradient-based separation (DGBS) over Ficoll-Paque using COBE 2991 (Terumo BCT) [3] or not [4,5]. Studies have demonstrated feasibility and clinically efficiencies for centrifugation using automated or semi-automated separator devices such as Haemonetics Model 30 [6], Amicus (Fresenius-Kabi) and Fenwal CS3000 Omnix plus devices [7] or COBE Spectra [3,8,9], albeit with some quantitative variations between methods for RBC depletion and

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hematopoietic progenitor cells (HPC) recovery. The newly available BMP kit (Bone Marrow Program) available with the Spectra Optia device achieve results in a similar range as those reported for Optia's predecessor technology, the COBE Spectra [10–13].

The Sepax-2 device (Biosafe SA, a brand of GE Healthcare, Geneva, Switzerland) is commonly used for cord blood banking [14], HPC concentration before cryopreservation [15] or HPC washing after thawing [16,17]. Due to the low capacity of the Sepax-2 spinning chamber (210 mL at each cycle), processing of bone marrow (BM) collection for adult HPC transplantation processing requires several centrifugation cycles thus limiting the use of Sepax-2 to mononuclear cells (MNC) isolation from low volumes bone marrow aspirates for regenerative medicine [18,19]. Up to now, density-free separations onto Sepax-2 device were performed using Generic Volume Reduction (GVR) software and CS-490 disposable kits. The GVR protocol allowed initial product volumes between 50 mL and 880 mL. Several procedures were required for larger BM volumes requiring BM splitting and extensive manipulation.

The recent introduction of the SmartRedux software only available with the Sepax-2 device provided the ability to process an input volume of up to 3300 mL in a single raw extending the use of the Sepax-2 device for preparations of BM for hematopoietic transplantations in adults. The procedure is adaptive and various settings can be settled to enhance cell recovery or deplete RBC contamination in the final product. Its performances for the processing (volume reduction or RBC depletion) of bone marrow with volumes higher than 880 mL are currently under evaluation.

Increasing regulations in cell therapy field requires that process validations shall be performed prior to their application to therapeutic products for HPC transplantation [20–22]. However, HPC collections dedicated to validations are not available. Cell therapy centers must demonstrate feasibility, reproducibility and clinically relevant efficiency for their procedures even if satisfactory performances are reported by the manufacturers. These validations must be performed using cellular products as close as possible to the therapeutic product in order to establish initial and final graft specifications demonstrating an "in-house" reproducibility for the procedure. They are usually performed using disqualified products issued from blood donation from healthy subjects such as buffy-coats (BC) because their physicochemical characteristics and cellular content are in the same range of those from the BM [10]. Nonetheless, as they originate from healthy donor's peripheral blood, BC contain CD34 + HPC quantities as few as 0,7 10^6 per BC [23]. Consequently, biological parameters studied to validate the process are white blood cells (WBC) or mononuclear cells (MNC) and not CD34 + HPC. Here, we report the capability to generate representative non-therapeutic products (NTP) close to BM harvest characteristics, significantly enriched with CD34 + HPC, by mixing several products issued from the preparation of random platelet concentrates (RPC) and disqualified BC.

Using these products, we settled optimal settings for SmartRedux (method A or SmartRedux-ABOi) to achieve in a raw extremely low residual RBC volumes together with high mononuclear (MNC) and hematopoietic progenitor cells (HPC, CD34 positive cells) recoveries. To validate its performance, we compare it with the automated method based on a density gradient based-separation (DGBS) over Ficoll-Paque using the NeatCell software (method B).

Materials and methods

Products characteristics

Buffy coats (BC) and residues from random platelet concentrates (RPC) from healthy donors were purchased from the French Blood Center (EFS, PACA-Corse, Marseille, France). BC and RPC were pooled (three to four pooled products each time) to generate initial products close to BM characteristics for transplantation. RPC provided high quantities of white blood cells (WBC) and several million of CD34 + HPC each. BC provided billions of RBC resulting in hematocrit (Hct) between 35% to 50%. (Table 1).

Separation device and protocols

Sepax-2 uses fully automatic walk-away software for volume reduction (SmartRedux) and RBC depletion (NeatCell) with the tubing sets CS490.1 and CS900.2 respectively (Biosafe SA), as described elsewhere [14–17]. Others reagents required for RBC depletion are Ficoll-Paque™ PLUS density gradient media (GE Healthcare, USA), 0,9% sodium chloride (B. Braun Medical Inc., USA) and 4% human serum albumin (HSA, LFB, Les Ulis, France).

The characteristics of the final product (total volume, optional additional volume of donor plasma) can be selected in SmartRedux software so as to better adapt the graft composition to the ABO compatibility status between donor and recipient, and allow a safe and easy infusion to the patient. Before starting the procedure, several settings must be adjusted by the operator. One major option is the capability to proceed using either a "fixed final volume" or a "proportional volume" method. Briefly, the former, the final volume can be selected by the user between 1 mL and 1500 mL, the latter, the final volume will be calculated as a percentage of the initial quantity of nucleated cells (between 1% and 100%) (see operating manual). Taken together, these parameters estimate a factor of volume reduction (Rf) for the SmartRedux procedure calculated as follows:

$$Reduction\,factor = \frac{Initial\,volume}{(final\,volume - volume\,of\,additional\,plasma)}$$

Previously, we validated SmartRedux software and applied our settings in BM processing for ABO-compatible (ABOc) transplantation, referred further as to SmartRedux-ABOc (data not shown). In all these procedures, we used the "fixed final volume" option and set a final volume below the reference limit of 10 mL/recipient body weight. This translated in a Rf for BM volume (ratio between the final and the initial volumes after BM filtration and dilution with anticoagulant additives) of 4,0 ± 0,9 fold. However, median RBC residual volume was to 158 ± 82 mL which prevent its use for major ABOi BM transplantation.

For major ABOi BM transplantation, following manufacturer's advice, we enhanced RBC depletion using SmartRedux software targeting a drastic reduction of the BC volume up to 7,5% of the volume of the initial product (method A, also referred as to SmartRedux-ABOi).

Method A was validated on eight NTP. We proceeded using the "fixed final volume" option, and set additional plasma to 1% of

Table 1
Products characteristics and performance data for method A and method B with pools of BC and residues of random platelet concentrates.

RBC depletion technology		Method A (n = 8)	Method B (n = 4)
Starting Product	Volume (mL)	1036 ± 194	884 ± 136
	WBC (10^9)	13,93 ± 4,27	21,87 ± 11,70
	Hematocrit (%)	36,8 ± 1,5	38,5 ± 2,4
	RBC volume (mL)	367 ± 67	342 ± 69
	Platelets (10^{11})	2,23 ± 0,29	2,29 ± 0,60
	MNC (10^9)	6,92 ± 1,98	17,21 ± 8,51
	CD34+ (10^6)	6,52 ± 1,44	10,91 ± 8,91
Final Product	Volume (mL)	82 ± 19	43 ± 2
	RBC volume (mL)	19,0 ± 8,4	1,6 ± 2,0
	RBC depletion (%)	95,3 ± 2,0	99,6 ± 0,4
	MNC recovery (%)	77,0 ± 15,1	58,2 ± 17,2
	CD34+ recovery (%)	86,4 ± 14,6	76,8 ± 9,3

All datas are presented as mean ± standard deviation.

initial product volume. Hematocrits of initial products were adjusted between 35% and 50% before processing if necessary. Median Rf of NTP volume was to 14,8 ± 2,3 fold (12,0 – 18,3) corresponding to 6,7% ± 1,1% of initial product volume.

We compared the efficiency of SmartRedux-ABOi (method A) with results from RBC depletion using an automated DGBS over Ficoll-Paque considered as the "gold standard" using NeatCell software on the same device (method B). Method B was conducted on four NTP as follows: in a first step, the volumes of NTP were exactly decreased to 120 mL using previously validated and described SmartRedux-ABOc procedure. Then, we applied to this intermediate BC the NeatCell software to deplete RBC. At the end, the mononuclear cells (MNC) were collected in a small volume (about 45 mL).

In both approaches, either saline, HSA or autologous plasma can be added to the product in order to decrease the product density before use.

Quality controls and calculations

Methods were compared in terms of MNC and CD34 + HPC recoveries, % of RBC depletion and RBC residual volume. Product specifications including WBC, MNC, platelet counts (Plt) and Hct (%) were assessed with an automatic hemocytometry (SE-5000® hematology analyzer, Sysmex, Norderstedt, Germany). CD34+ cells were enumerated by flow cytometry using the single platform BD Stem Cell Enumeration Kit on a FACSCanto II flow cytometer (Becton-Dickinson, Les Ulis, France), as previously described [24]. Products volumes were calculated as weight × 1,05 (correction factor for product density). Total RBC volumes were calculated as product volume multiplied with Hct value. MNC, CD34 + HPC recoveries and Plt depletion were calculated from the quotient of post- and pre-process cell quantities. RBC depletion was calculated from the quotient of post- and pre-process RBC volume.

Processing time

For method A, processing time was calculated as the time from CS600.1 tubing set installation onto the Sepax-2 device (hands-on) to the completion of the "in-house" optimized settings of SmartRedux software (walk-away). For method B, processing time started with CS600.1 tubing set installation onto the Sepax-2 device, application of standard SmartRedux software and then followed with CS900.2 kit installation and application of NeatCell

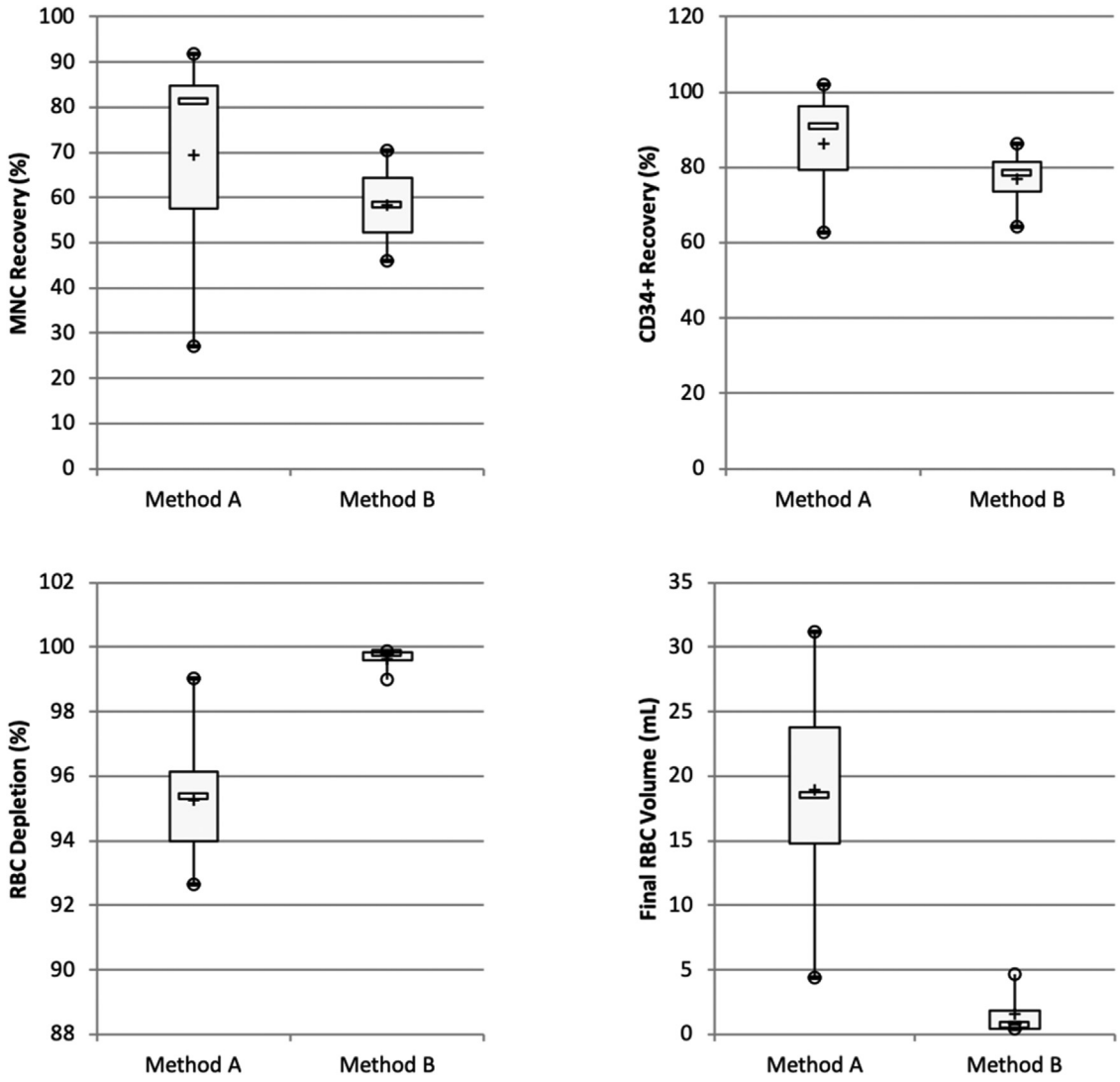

Fig. 1. Performance data. MNC (upper left) and CD34 + HPC (upper right) recoveries, RBC depletion (lower left) and Residual RBC volume (lower right) using either "in-house" settings of SmartRedux software (method A, n = 8) or the association of SmartRedux endpoint volume of 120 mL and NeatCell software (method B, n = 4). Data are shown in box & whiskers plots showing min, max, median (□) and mean (+).

program. During automatic process steps none operator was mandatory (walk away).

Statistical analysis

Statistical analysis were performed using BiostaTGV website (Institut Pierre-Louis en Epidémiologie et Santé Publique, Paris, France). Results obtained with method A and method B were statistically compared using a non-parametric Wilcoxon–Mann Whitney test for unpaired samples.

Results

Feasibility

All runs were successful and uneventfully excepted one for method B where the standard SmartRedux failed and was reinitiated with a new tubing set.

Characteristics of BC pools are given in Table 1. Although we did not split products such as for cross-validation assays, the volumes, Hct, WBC and Plt contents of all the starting products were very similar for both methods introducing no bias into the interpretation of the data.

The microbiological controls performed on initial and final products for both methods (A & B) were all negative.

Performances (recoveries and depletions)

For both methods, a very drastic RBC depletion was achieved with a median of 95,4% (range: 92,7–99,0%) and 99,8% (99,0–99,9%) for method A and method B, respectively (Fig. 1). However, the median residual RBC volume in the final product was significantly higher ($p < 0,05$) using method A, 19 mL (4,4–31,2 mL) than method B, 0,7 mL (0,4–4,7 mL) (Fig. 1).

For CD34 + HPC, method A and method B achieved a satisfactory recovery with a median of 90,9% (62,7%–102,1%) and 78,4% (64,1–86,2%) respectively ($p > 0,05$) (Table 1).

Method A provided a median WBC recovery of 80,9% (45,6%–87,3%) while WBC recovery with method B was significantly lower, 40,1% (29,0–60,3%) ($p < 0,05$). MNC recoveries were 81,3% (46,9%–91,9%) for method A and 58,2% (46,1–70,4%) for method B, respectively (Fig. 1) but MNC purity on the final product was significantly higher ($p < 0,05$) in products processed with method B (median 70,0%; range: 61,0–74,0%) than those resulting from method A (median 55,0%; range: 47,1–63,3%). This difference is due to the additional polymorphonuclear cells depletion provided by Ficoll-Paque used in method B which improves the MNC purity.

Finally, a robust and significantly higher ($p < 0,05$) platelet depletion was observed for method B than for method A with a median of 89,8% (88,5–92,4%) versus 16,6% (10–42,7%), respectively.

Process duration and time consumption

Process duration and labor intensity were also analyzed (Table 2). For both methods, one operator was needed all along the process. The median total processing time was 174 min (126–218 min) and 291 min (275–324 min) for method A and method B, respectively. Time duration of method A is significantly ($p = 0,004$) shorter than method B.

Table 2
Process duration for method A ("in-house" Optimized settings of SmartRedux software) and method B (endpoint volume of 120 mL SmartRedux and NeatCell software).

	Method A (n = 8)	Method B (n = 4)
Optimized / Standard SmartRedux hands-on	36 ± 12	44 ± 8
Optimized / Standard SmartRedux walk-away	132 ± 25	104 ± 11
NeatCell hands-on	N/A	65 ± 10
NeatCell walk-away	N/A	82 ± 4
Total Process Duration	168 ± 29	295 ± 21

All durations are expressed in min and are presented as mean ± standard deviation.

Discussion

Increasing regulations in cell therapy requires that process validations should be performed prior to their application to therapeutic products for HPC transplantation. Due to the invasiveness of the bone marrow collection, it is clear that the amount of BM available to perform process validations is very limited, and in no way the GMP-required performance qualifications of new technologies in cell therapy center can be completed with therapeutic BM collections. Buffy coat or blood donation products are suitable replacement for process validation as previously reported [10]. Although leukocyte populations differ between BC and BM, bone marrow containing fewer lymphocytes and more immature myeloid cells, hematocrit and white blood cell concentration are in the same range. Although sedimentation properties differ between BM and BC, CD34 + HPC and MNC recoveries do not appear to be affected. We confirmed in this study that BC are suitable for qualifications and that enrichment with residues from RPC containing HPC allows the qualification of the method by monitoring in non-therapeutic products, the relevant target cell for BMT instead of WBC or MNC.

Sepax-2 device is used in cord blood banking [17], BM cell concentration and MNC isolation for regenerative medicine [18,19]. In the past few years, volume reduction of HPC before cryopreservation [15], HPC washing after thawing [16,17] have been evaluated using Sepax-2. Few data were published on the processing of high volume of products enriched in MNC and CD34 + HPC such as those aimed for BMT in adults.

Our work demonstrated the capability of Sepax-2 and SmartRedux software for high RBCs depletion of high volume products in a raw and without the use of a density gradient separation. Excellent recoveries of MNC and CD34+ cells (81,3% and 90,9%, respectively) associated with a high RBC depletion (95,4%) could be achieved using our "in-house" SmartRedux settings (method A). Residual RBC volumes, spanning from 4,4 to 31,2 mL, are in concordance with published recommendations for major-ABOi transplantation in adult patient, many authors estimating 30 mL as the upper limit to infuse in adults [1,2]. No safe quantity of RBC below which hemolytic reaction will not occur does exist even if Rowley and colleagues published no clinically significant hemolysis only when infusing less than 15 mL of residual RBC [25]. Our data are comparable to results obtained with another ficoll-free devices such as COBE Spectra [3,8,26] or the newly introduced Spectra Optia although with the latter, a very trained and experienced staff could obtain a slightly lower residual volume of red blood cells (rather around 5–15 mL) [11–13].

Moreover, duration of method A was 174 min in the same range of the Optia procedure (135 min) [10] compatible with excellent cell viability and would not delay transplantation procedure with an additional processing time. Not surprisingly, method B took a longer time (292 min), similar to the COBE 2991 procedure (300 min) because this method required a slow deposit of the cell layer onto the Ficoll-Paque firstly introduced into the processing kit. Compared to RBC depletion using the COBE 2991 device [3,10], due to the low capacity of the Sepax-2 spinning chamber, the processing with method B required at first a volume reduction to 120 mL (SmartRedux ABOc) before the NeatCell procedure, doubling the operator time.

We achieved a higher RBC depletion using method B, inferior to 5 mL, but lowered MNC and CD34 + HPC recoveries, a trend previously reported comparing DGBS on Ficoll-Paque using COBE 2991 and Sepax-2 [10]. Consequently, we decided to apply NeatCell only in situations requiring a drastic RBC depletion inferior to 5 ml. This includes major ABOi BMT in very young pediatric recipients where the volume of the graft is limited due to low body weight of the patient and adult recipients with anti-A or anti-B antibodies titers exceeding 1:32 [2].

Conclusions

We showed that “in-house” SmartRedux-ABOi with a drastic volume reduction factor (method A) as well as “gold standard” automated DGBS over Ficoll-Paque using NeatCell software (method B) achieved satisfactory RBC depletion and CD34+ recovery. We demonstrated that the use of Sepax-2 device should not be restricted to small-volume BM cell processing and in association with SmartRedux software can be used for RBC depletion in large-volume BM in a raw without the need to proceed to a DGBS. The choice between one option or the other should be guided by the need to reach a very low amount of residual RBC or to promote the highest progenitor CD34+ recovery. Further validations using BM of our “in-house” SmartRedux-ABOi protocol are needed to confirm our data but we suggest to use it for BM processing in major ABO-incompatible BMT in adult recipients rather than DGBS over Ficoll-Paque which is time consuming and costly. Moreover, either for SmartRedux or NeatCell software, BM processing with Sepax2 is fully automated and can be performed securely and easily by a well-trained staff.

Conflicts of interest

Authors declare no conflicts of interest.

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