SPECTRA OPTIA® APHERESIS SYSTEM WITH CONTINUOUS MONONUCLEAR CELL COLLECTION (CMNC)

Literature Summary

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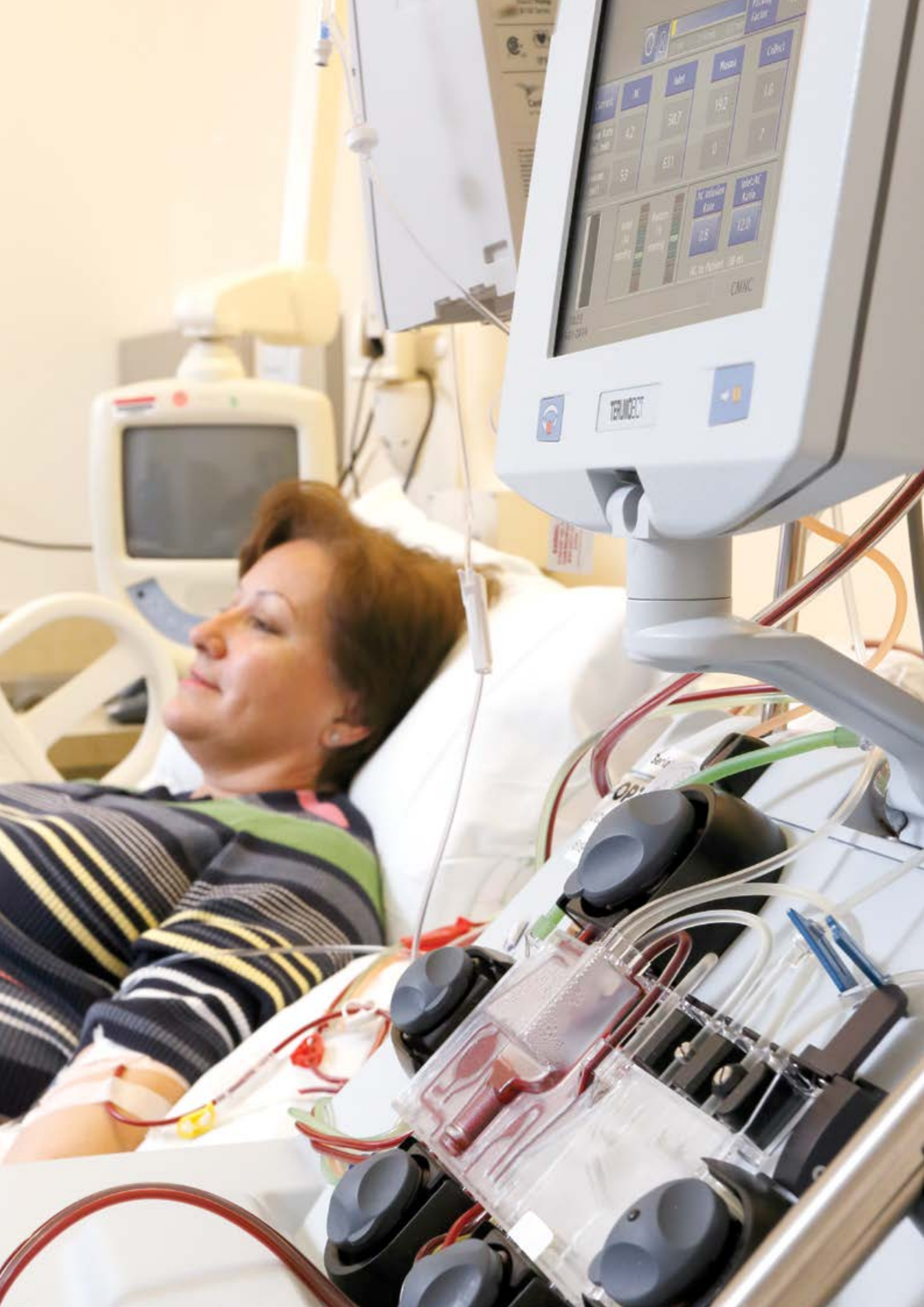

HISTORICAL BACKGROUND

Apheresis-based collection of mononuclear cells (MNCs) is a common method to obtain suitable fractions of CD34+ cells for autologous or allogeneic hematopoietic stem cell transplantation. The COBE® Spectra Apheresis System was widely used and earlier described as the "gold standard" for MNC collections. In 2009, the Spectra Optia system with the MNC collection protocol was introduced with a collection method distinct from the COBE Spectra system. In this literature review, comprised of all available abstracts as of October 2015 pertaining to the Spectra Optia system CMNC protocol, we describe results from this Spectra Optia system protocol, which operates in a similar way to the MNC protocol on the COBE Spectra system.

Initially conceived as a method for fast and effective therapeutic leukodepletion in leukemia patients suffering from leukostatic events (blast crisis), the Spectra Optia system's white blood cell depletion (WBCD) protocol with (IDL) tubing set was found to also collect CD34+ cells from mobilized subjects. A prospective randomized clinical trial* compared this new IDL-based approach versus the Spectra Optia system with the MNC protocol for collection of mobilized peripheral blood stem cells (PBSCs) from allogeneic donors. This study completed enrollment and data collection in November 2014, and a manuscript is in preparation.

$$CE1\ (\%) = \frac{\#\ \text{cells in product}}{\left[\frac{\text{pre-count} + \text{post-count}}{2}\right] \times V_{\text{blood processed}}}$$

$$CE2\ (\%) = \frac{\#\ \text{cells in product}}{\text{pre-count} \times V_{\text{blood processed}}}$$

Simultaneously, the Spectra Optia system's WBCD protocol was independently applied in ten procedures to collect PBSCs for autologous stem cell rescue from nine mobilized patients (four non-Hodgkin's lymphoma [NHL], three multiple myeloma [MM], one amyloidosis, one acute non-lymphoblastic leukemia) (Table 1).[1] Collection efficiencies (CE1)[a] of CD34+ cells were 60.6% in NHL (n = 4) and 72.8% in MM (n = 3). Compared with CE1 values from historical data on the COBE Spectra system, 33% (NHL, n = 18) and 42% (MM, n = 23), this approach seemed to yield higher efficiencies, although the relatively small sample size must not be overlooked. Being conducted without observing any adverse side effects, these seminal studies gave rise to the development of the Spectra Optia system configured for a continuous MNC harvesting protocol known as the CMNC protocol. Initial abstracts further report on comparative analyses between this recently developed protocol and other existing systems. This review summarizes preliminary results obtained using the Spectra Optia system with the CMNC protocol.

CMNC COLLECTIONS IN A MOBILIZED SETTING

The Spectra Optia CMNC protocol was CE marked and became available in some world areas in 2014. Post-market studies have been conducted to assess the performance of this continuous-flow protocol. A comparison of the Spectra Optia CMNC protocol with the Fenwal™ Amicus™ system was performed retrospectively in two patient groups (26 MM and 14 NHL patients) that were matched for diagnosis, pre- and post-apheresis white blood cell (WBC) count, CD34+ yield and processed blood volume. Collection efficiency for CD34+ cells, calculated as CE2[b] and expressed as mean ± standard deviation (SD), was found to be significantly higher in the Spectra Optia system with the CMNC protocol, 50.2% ± 11.22%, than in Amicus, 37.0% ± 14.8%, ($p = 0.004$ t-test). In summary, the authors concluded that both systems are safe and effective.[2]

An abstract by Lamb and Stevens, presented at the 41st Annual meeting of the European Society for Blood and Marrow Transplantation (EBMT 2015), summarizes a retrospective analysis of 40 apheresis collections which used the CMNC protocol on the Spectra Optia system.[3] This series of collections had CE, ease of collection and product purity as primary objectives. Collec-tions originated from 25 mobilized individuals, 23 patients (15 MM, one sarcoma and seven lymphoma patients), and two donors, with extended ranges of CD34+ and WBC counts before apheresis. The applied mobilization regimen comprised of cyclophosphamide + granulocyte-colony stimulating factor (G-CSF) (n = 7), hyper-CVAD + G-CSF (n = 1), ICE/RICE + G-CSF (n = 9) or G-CSF alone. A median CD34+ CE2 of 52% and a median CD34+ dose of 2.5 × 10^6 cells/kg (range 0.45 to 27.39 × 10^6/kg) were obtained.[3] The median collected product volume was 268 mL (range 114 mL to 389 mL).

Marculescu, et al. and Tonev, et al. also report on mobilized, predominately autologous, collections using the CMNC protocol.[4,5] Diverse mobilization strategies were applied on nine patients and one donor by Marculescu and colleagues: six MM patients received cyclophosphamide + G-CSF (one patient was mobilized twice due to a poor response); one Hodgkin's lymphoma patient received IGEV + G-CSF; and one Ewing's sarcoma patient received cyclophosphamide + etoposide + G-CSF. The one allogeneic donor was mobilized with G-CSF only. Large blood volumes were processed in most procedures (9,256 mL to 18,052 mL), with a low median platelet CE1 of 12.8% (range 8.3% to 20.9%). Acceptable levels of CD34+ cells were found. The median collection efficiency was 47.4% (34.4% to 56.5%). A median CD34+ dose of 7 × 10^6/kg (2.8 to 8.11 × 10^6/kg) was collected. In addition, the authors found a positive correlation between CD34+ counts before apheresis and CD34+ yield per processed blood volume ($R^2 = 0.76$), suggesting the potential of pre-apheresis CD34+ cell counts as a predictor of the blood volume to be processed in order to achieve the targeted yield of CD34+ cells.[4]

Tonev and colleagues investigated the performance of the Spectra Optia system with the CMNC protocol in a population of 11 patients.[5] Prior to apheresis, eight patients were mobilized using high-dose chemotherapy + G-CSF, while the three remaining patients received G-CSF only (one of which received Plerixafor). The authors then identified two patient groups according to their CD34+ counts before harvesting: they were termed the "good mobilizer" group of seven patients (CD34+ count, 421/µL ± 93.9/µL), and the "poor mobilizer" group of four patients (CD34+ count, 30/µL ± 5/µL). After processing a total blood volume of 8.1 L ± 0.9 L, the CD34+ CE2 for the good mobilizers was 36.2% ± 5.6%. On the other hand, in the poor mobilizer group, where a higher CD34+ collection efficiency is needed, a higher value of 47.5% ± 4.6% was observed.

**optiMaL ClinicalTrials.gov Identifier: NCT01901458, principal investigator: Dr. Johannes C. Fischer, Heinrich-Heine University, Düsseldorf, DE.*

However, the difference between both groups was not significant ($p > 0.1$). The authors explain the higher $CD34^+$ CE in the poor mobilizer group as possibly resulting from the additional dose of G-CSF, administered one hour after the start of apheresis. The Spectra Optia system with the CMNC protocol runs resulted in a $CD34^+$ dose of $8.7 \pm 2.1 \times 10^6$/kg. In addition, a platelet loss of 16.7% ± 3.4% was reported. The authors further concluded that the CMNC protocol is applicable and efficient in a wide range of $CD34^+$ pre-count situations with limited platelet contamination in the collected product. They also suggested an increase in collect pump flow rate to increase $CD34^+$ CE values.

Although preliminary, these initial abstracts describe adequate performance of the Spectra Optia system with the CMNC protocol on donors and patients with diverse pathologies, with varying mobilization regimens and performed without any reported adverse events.

IMPACT OF COLLECT PUMP FLOW RATE ON YIELD AND PRODUCT VOLUME

Product volume considerations after $CD34^+$ collections are often important. The overall infusion volume to the patient and the amount of dimethyl sulfoxide (DMSO) used for cryopreservation are factors that contribute to the usefulness of the reinfused product. A minimal product volume reduces patient exposure to high amounts of DMSO. In recent work by Watts M, et al., the collect pump flow rate in the Spectra Optia system with the CMNC protocol was directly manipulated to minimize the final product volume.[6] A total of 50 procedures were assigned to three groups with different collect pump flow rates; that is, the default 1.0 mL/min (n = 16), and two reduced flow rates of 0.8 mL/min (n = 13) and 0.6 mL/min (n = 21), respectively. As anticipated, median product volumes decreased significantly in correlation with decreasing collect pump flow rates (192 mL, 156 mL and 112 mL for 1.0 mL/min, 0.8 mL/min and 0.6 mL/min, respectively). This permitted immediate cryopreservation. In parallel, median $CD34^+$ CE2 levels slightly dropped from 54% at 1.0 mL/min over 44% at 0.8 mL/min to 43% at 0.6 mL/min. Only the drops from 1.0 mL/min were statistically significant ($p = 0.006$ from 1 mL/min to 0.8 mL/min and $p = 0.01$ for 1 mL/min to 0.6 mL/min; Mann–Whitney U test). However, the reduced collection efficiencies at 0.8 mL/min and 0.6 mL/min were equivalent to those seen in previous experience with the COBE Spectra system's AutoPBSC protocol, which served as the comparator in this volume-reduction study. Furthermore, the overall aim of achieving a dose sufficient for engraftment was still accomplished. The median engraftment time was 11 days for both ANC to 0.5×10^9/L and platelet count to 20×10^9/L. Finally, Watts et al. reported on a remarkable consistency of the results achieved even with an apheresis staff as high as 12 nurses.[6] The authors concluded that, despite the risk of moderate loss of $CD34^+$ cells, a highly enriched, low-volume $CD34^+$ product can be obtained by manipulation of the collect pump flow rate.

CMNC COLLECTIONS IN A NON-MOBILIZED SETTING

Punzel and colleagues performed a prospective study of allogeneic apheresis collections for donor lymphocyte infusion (DLI), comparing the Spectra Optia system with the CMNC protocol (n=17) with the Spectra Optia system with the MNC protocol (n=18).[7] Similar collection efficiencies for lymphocytes, MNCs, T-cell fractions, B-cell fractions and NK-cell fractions were reported. In addition, equal MNC purities in the product (CMNC 85.3% ± 9.9%, MNC 87.2% ± 3.5%) were obtained. Significantly lower product volumes were obtained using the Spectra Optia system with the CMNC protocol compared to the Spectra Optia system with MNC protocol (176 mL ± 54 mL and 238 mL ± 47 mL respectively, $p < 0.005$). This was attributed to a significantly higher volume of blood processed on the Spectra Optia system with the MNC protocol. Furthermore, processing throughput (defined by the authors as Ly/kg donor/minute/peripheral blood) tends to be higher with the CMNC protocol, resulting in shorter procedure times to collect similar amounts of MNCs (Table 2).

In a comparison with three other systems—that is, the COBE Spectra system, the Spectra Optia system MNC (both manufactured at Terumo BCT, Lakewood, CO, USA) and Amicus (Fresenius Healthcare)— the Spectra Optia system with the CMNC protocol was assessed based on the CE1 of monocytes and lymphocytes (MNCs), hemoglobin (Hb) contamination of the product and procedure time (Table 2). This work, reported by Robitzsch, et al., gathered data from 268 procedures, generated from 62 healthy donors and 116 patients without mobilization.[8] MNCs were efficiently harvested using the Spectra Optia system with the CMNC protocol, which also demonstrated the fastest collection, as expressed as the number of MNCs collected per minute (Table 2). Platelet CE1 levels were lower with the Spectra Optia system with the CMNC protocol and Amicus than with the Spectra Optia MNC and Cobe Spectra. All devices generated similar lymphocyte CE levels. However, a lower monocyte CE1 was observed on Amicus in comparison with the Spectra Optia system with the CMNC protocol, the Spectra Optia system with MNC protocol and the COBE Spectra system (Table 2). The authors concluded that the Spectra Optia system CMNC outruns the COBE Spectra system with regards to MNC CE, product purity and procedure time.

CONCLUDING REMARKS

In summary, initial data indicate that the Spectra Optia system with the CMNC protocol is a suitable alternative for apheresis-based MNC and $CD34^+$ collection with regard to efficiency, yield and purity. Based upon a continuous collection flow technology, the procedure time is minimized in comparison with intermittent-flow devices, with limited platelet loss in the product. No adverse events were reported for any procedure, however; most abstracts did not discuss adverse events. Reported engraftment times were adequate. Furthermore, customized collect pump flow rates were shown to reduce product volumes with limited proportional loss of efficiency.

Abbreviations: CVAD = cyclophosphamide, vincristine, doxorubicin, IGEV = ifosfamide, gemcitabine, vinorelbine and prednisone, ANC = absolute neutrophil count, Ly=lymphocytes

Table 1: *Mobilized CMNC collections*

Variable	Spectra Optia System IDL Set	Spectra Optia System with the CMNC Protocol					Amicus
	Lozano[1]	Gumogda[2]	Lamb[3]	Watts[6]	Marculescu[4]	Tonev[5]	Gumogda[2]
Number of procedures	10	20	40	50	10		
Number of patients	9	20	23	41	9	11	20
Number of donors	0	0	2	0	1	0	0
Pre-CD34⁺ (cells/µL)	40.2 [12.0–252.9]		39.2 [7–466]			30 ± 5 (poor mobilizer) 421 ± 94 (good mobilizer)	
Pre-WBC* (× 10⁶/mL)			35.9 [4.0–69.6]			38.6 ± 4.9	
CD34⁺ CE1 (%)*	60.7 [40.5–90.1]						
CD34⁺ CE2 (%)*		50.2 ± 11.2	52 [29-114]	54 [50–62] at Qcol of 1 mL/min 44 [41–47] at Qcol of 0.8 mL/min 43 [38–52] at Qcol of 0.6 mL/min	47.4 [34.4–56.5]	47.5 ± 4.6 (poor mobilizer) 36.2 ± 5.6 (good mobilizer)	37.04 ± 14.8
PLT CE1 (%)*					12.8 [8.3–20.9]		
PLT loss (%)						16.7 ± 3.4	
CD34⁺ yield (× 10⁶/kg)			2.5 [0.45–27.39]		7 [2.8–8.11]	8.75 ± 2.11	
RBC* (mL)					3.7 [1.4–6.5]		
Volume (mL)	191 [146–257]		268 [114–389]	192 [191–194] at Qcol 1.0 mL/min 156 [152–157] at Qcol 0.8 mL/min 112 [111–113] at Qcol 0.6 mL/min		164.4 ± 0.02	
Number TBV* Processed	3.3 [1.7–4.7]	2.5					2.5
Volume WB* Processed					9,256–18,052	8,090 ± 900	
Procedure time (min)	210 [111–293]			200			

(*) Abbreviations: CE: collection efficiency; PLT: platelets; TBV: total blood volume processed; WBC: white blood cells. ICE/RICE = Rituximab, Ifosfamide, Carboplatin, Etoposide

Empty cells indicate that no data was available for the studied variable.

Table 2: *Non-mobilized CMNC collections*

Variable	Spectra Optia System CMNC Protocol		COBE Spectra System	Spectra Optia System MNC Protocol		Amicus
	Robitzsch[8]	Punzel[7]	Robitzsch[8]	Robitzsch[8]	Punzel[7]	Robitzsch[8]
Number of procedures	20	17	177	31	18	40
Lymphocyte CE1 (%)	56 ± 17	60.0 ± 13.3	62 ± 10	54 ± 19	64.4 ± 14.8	57 ± 19
Monocyte CE1 (%)	65 ± 15		58 ± 19	61 ± 21		39 ± 16
MNC CE1 (%)	64 ± 11		57 ± 19	55 ± 17		52 ± 16
MNC Purity (%)	90 ± 7	85.3 ± 9.9	75 ± 16	92 ± 7	87.2 ± 3.5	96 ± 3
Volume (mL)		176 ± 54			238 ± 47	
Throughput (MNC × 10^6/min)	69 ± 34		56 ± 26	57 ± 22		53 ± 25
AE	Not Reported	Not Reported	Not Reported	Not Reported	Not Reported	Not Reported

Empty cells indicate that no data was available for the studied variable.

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