Collection of WBC-reduced single-donor PLT concentrates with a new blood cell separator: results of a multicenter study

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BACKGROUND: A new cell separator (COM.TEC, Fresenius) was recently developed aimed at efficient collection of WBC-reduced single-donor PLT concentrates (SDPs).

STUDY DESIGN AND METHODS: Five German centers collected 554 WBC-reduced SDPs with help of the COM.TEC cell separator. Two multicenter cell counting studies were performed at the beginning and at the end of the study to document uniform counting results among the participating centers.

RESULTS: A total of 441 (79.6%) PLT collections were included in the study according to the protocol. A total of 342 single-dose and 99 double-dose SDPs were collected. For single-dose SDPs, an average blood volume of 2826 ± 409 mL was processed in a donation time of 55 ± 11 minutes. Mean PLT yield of these products was $3.11 \times 10^{11} \pm 0.40 \times 10^{11}$ and the WBC contamination was $0.11 \times 10^{6} \pm 0.20 \times 10^{6}$. For double-dose SDPs (PLT count, $5.29 \pm 0.93 \times 10^{11}$), 3943 ± 639 mL was processed. The average difference between the target and the collected PLT concentration was –2.8 ± 12.0 percent for single-dose SDPs and –1.8 ± 9.5 for double-dose SDPs, respectively. The collection efficiency was 53.7 ± 5.8 percent for single-dose SDPs and 58.2 ± 6.2 percent for double-dose SDPs. If all results of each sample from the counting study were set to unity (to the mean over all centers), most PLT determinations were very similar to the mean, for example, near or 1 if set to unity.

CONCLUSION: The COM.TEC machine makes it possible to obtain WBC-reduced SDPs that comply with current standards.

Low WBC contamination of single-donor PLT concentrates (SDPs) can be achieved either by filtration or directly during PLT collection using special apheresis techniques.[1-9] These preparative apheresis techniques use the fluidized particle bed technology,[1-3] the elutriation principle,[4-8] or the technique of periodically alternating interface position[9] for WBC reduction of SDPs. Filtration results in a PLT loss of approximately 10 to 15 percent, includes the risk of filter failure, and if carried out after the apheresis procedure, is cumbersome and costly.

To avoid the problems associated with filtration, a new cell separator has recently been developed (COM.TEC, Fresenius, Bad Homburg, Germany), designed to collect WBC-reduced SDPs without filtration. The COM.TEC device uses plasma recirculation for obtaining a constant Hct in the separation chamber resulting in PLT concentrates with high yields and low WBC contamination. This study reports on the results of a multicenter study with the new cell separator.

ABBREVIATION: SDP(s) = single-donor PLT concentrate(s).

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MATERIALS AND METHODS

Donors

Donor eligibility according to the German guidelines and recommendations for cytapheresis was the primary inclusion criterion.[10,11] Furthermore, a body weight of greater than 50 kg, PLT values of 180 to 350 per nL, Hb level of at least 12.5 g per dL in women and at least 13.5 g per dL in men, RBC count greater than 4.00 per pL, and WBC count less than 10.0 per nL were required according to the study protocol. Donors with PLT baseline values of 180 to 280 per nL underwent a single-dose SDP collection with a target yield of 3.0×10^{11} to 3.3×10^{11} PLTs per unit. Donors with PLT counts greater than 280 per nL were assigned to donate a single dose or a double dose with greater than 4.4×10^{11} PLTs per unit. Exclusion criteria were first-time donor status and plateletpheresis within the past 14 days. All donors gave written informed consent before the apheresis procedure.

Cell separator

The blood cell separator was used in accordance with the manufacturer's instructions using the dual-needle plateletpheresis program (PLT5d DN). The device is equipped with a new separation chamber (C5) that is shaped like continuous spirals with a flow path interrupted by a built-in barrier (Fig. 1). The donor blood flow is automatically adjusted to donor's height and body weight. An additional pump makes it possible to maintain a constant Hct level in the separation chamber by plasma recirculation (Fig. 2). The flow rate of plasma recirculation is dependent on the Hct level of the donor before the procedure, the blood flow, and the anticoagulant flow rate. The PLT separation is completely automated using a CCD camera, which detects the interface position at every revolution in the separation chamber. Deviations are compensated by changing the plasma flow rate. There is a short dwell time inside the centrifuge, and the PLTs are removed from the centrifuge as they are collected. The device uses the PLT-disposable C5L with two storage bags wherein PLTs can be stored for up to 5 days. The centrifugation speed was 2200 rpm, resulting in a gravity force of $578 \times g$ at the whole blood-port and $740 \times g$ at the PLT port. Within a scale of 1 to 56, the interface was set to 31.

The endpoint was automatically set by the cell separator according to the entered target PLT yield for a single-dose or double-dose SDP depending on the donors' baseline PLT count. For this purpose, donors' height, weight, PLT count before apheresis, and Hct level were entered into the computer of the cell separator, and the machine calculated the performance of the apheresis procedure (blood flow, anticoagulant flow, anticoagulant-to-whole blood ratio, time).

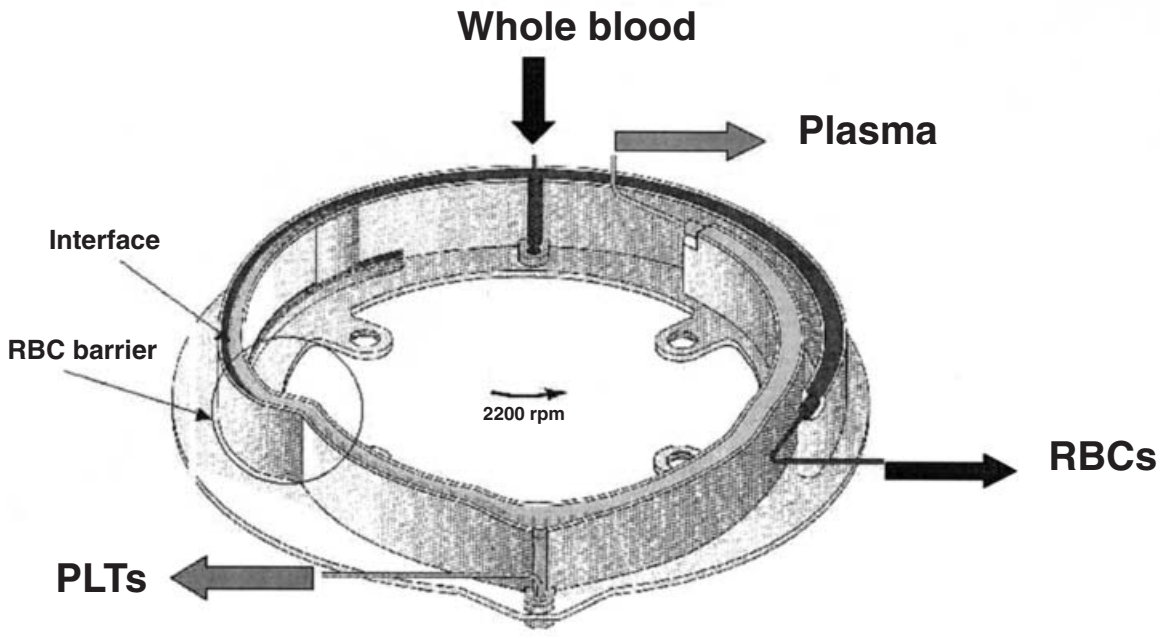

Fig. 1. New C5 separation chamber. Anticoagulated whole blood enters the separation chamber and is separated into its components by centrifugation. The interface position is automatically detected by a CCD camera of the cell separator. Deviations are compensated by changing the plasma flow rate. RBCs and WBCs cannot cross an angle, which is integrated in the separation chamber (RBC barrier), and exit the chamber via the RBC port. Plasma and PLTs cross the RBC barrier and are separated at the PLT port. PLTs are pumped into the storage bag while plasma exits the chamber via the plasma port.

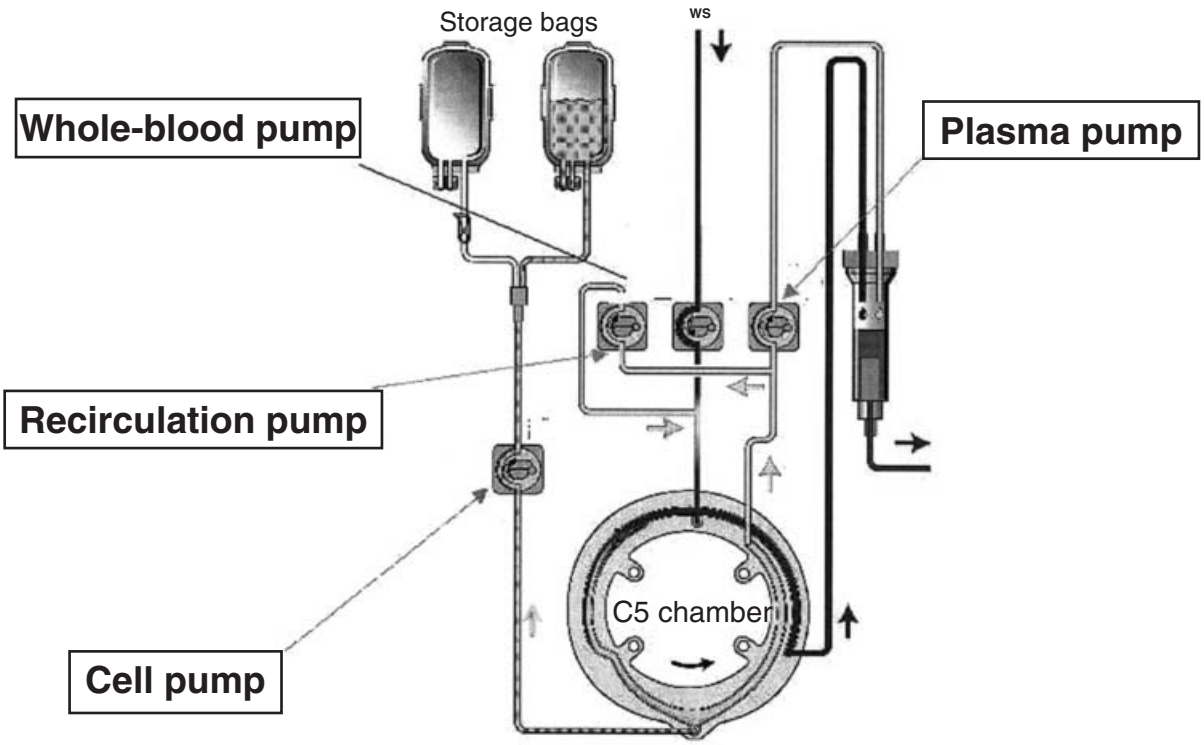

Fig. 2. Plasma recirculation. One part of separated plasma in the chamber is returned to the donor via the plasma pump, while the other part is recirculated via the recirculation pump in the separation chamber. Thereby a constant Hct level is maintained in the separation chamber during the whole course of the apheresis procedure.

TABLE 1. Code number of the participating university centers, total number of procedures, number of evaluable procedures according to study protocol, percentage of male donors, and donor age

Center code	Total number of procedures	Number of evaluated procedures (%)	Male donors (%)	Age (years)*
A	54	45 (83.3)	66.7	40.0 ± 9.6
B	52	40 (76.9)	80.0	41.9 ± 12.6
C	75	60 (80.0)	76.7	NA
D	135	99 (73.3)	99.0	37.0 ± 9.8
E	238	197 (82.8)	74.6	31.7 ± 9.2
Sum/cumulative mean	554	441 (79.6)	80.0	35.1 ± 10.5

* Mean ± SD.

Participating centers and cell counting study

Five university transfusion services participated in this multicenter study. A code number for each center and the number of plateletpheresis procedures performed are shown in Table 1. At the beginning and at the end of the multicenter study, Center D mailed three blood samples to the participating centers. Center D also mailed the samples to itself to avoid a possible systematic deviation by mailing. One sample was drawn from peripheral donor blood, and the two others from SDPs, one of which was spiked with WBCs.

Cell counting methods

Complete blood counts were performed on donors' samples before and after apheresis and in SDPs using an automated cell counter. Centers A and B used one cell counter (T660 and AcT diff, Coulter Electronics, Krefeld, Germany), and Centers C through E used another (Sysmex K-1000 and K-4500, TOA Medical, Kobe, Japan). In Centers A, C, and E, the residual WBC concentration in the SDPs was determined by the method of Masse et al.[12] with the following modifications: samples were diluted 1 in 5 with Türk's solution (Merck, Darmstadt, Germany). To allow the staining of the WBCs, the sample was incubated for at least 10 minutes at room temperature. An aliquot was placed in a modified Nageotte chamber and allowed to settle for 10 minutes before counting. Counting was performed by light microscopy with a 20× objective. Two grids were always evaluated (80 lanes, 100-µL diluted sample), except when already 10 or more cells were counted in the first grid (40 lanes). One cell observed in

both grids of the Nageotte chamber corresponds to 0.05 WBC per µL.

Centers B and D used a WBC counting kit (Leuco-COUNT, Becton Dickinson, Heidelberg, Germany) for flow cytometric analysis of WBCs. A 100-µL sample was added to a tube used for absolute WBC counting (TruCOUNT, Becton Dickinson) containing a definite number of beads. The sample was incubated with 400 µL of the Leuco-COUNT reagent in the dark at room temperature for 5 minutes. A flow cytometer (FACSCalibur, Becton Dickinson) was used to create a dot plot (fluorescence 1 vs. fluorescence 2). Two regions were created, one for the beads and one for the WBCs. All events were acquired and stored. When 10,000 events had been collected in the bead region, data acquisition was stopped. Region statistics on sample data were obtained, and calculations were performed as follows: The absolute number of residual WBC was determined by dividing the number of WBC events acquired by the number of fluorescent beads acquired and multiplying this result by the bead concentration.

For RBC counting the method of Müller et al.[13] was used. Basically, samples were diluted 1 in 10 with Hayem's solution (Merck, Darmstadt, Germany). After incubation of an aliquot in a moist atmosphere, RBCs were counted microscopically in the Neubauer chamber. Four large squares of the chamber were counted. One cell observed corresponds to 25 RBCs per µL.

Statistical analysis

The results are given as mean and SD. Fisher's exact test was used to examine associations in r × s tables. A rank-sum test was used to compare statistical differences between two independent groups and a signed-rank test was performed to compare statistical differences between two dependent groups for continuous measurements. The Kruskal-Wallis test was used to compare the differences between several independent groups. For comparison of the results obtained in the multicenter counting study, the counted values of the participating centers were divided by the mean of all centers. By "setting to unity" in this way an optimal value would be 1. A one-sample t test was used to compare a continuous measurement of one sample with a given value.

The collection efficiency (CE) was calculated as follows:

$$\mathrm{CE}(\%) = \frac{\text{PLT yield } (\times 10^{11}) \times 100}{\text{Mean PLT count } (\times 10^{9}/\mathrm{L}) \times \text{blood volume processed (mL)}}.$$

The mean PLT count was calculated from the counts obtained before and after apheresis. The blood volume processed was the processed volume minus the anticoagulant volume.

RESULTS

A total of 554 separations were performed; 441 (79.6%) of these could be included in the evaluation. The various reasons for exclusion of 123 (21.8%) procedures were as follows: technical problems (n = 44) such as software errors and watchdog alarms; PLT (n = 28), RBC (n = 7), and WBC (n = 12) values before apheresis out of normal range; multiple donations within 14 days (n = 15); Hct deviation before and after apheresis of greater than 5 percent (n = 15); and premature termination owing to problems with the venous access (n = 6). Several cases had to be excluded according to two of these reasons.

Donor characteristics

Age and sex of included donors were not equally distributed between the centers (Table 2). However, there are no statistical differences between included and excluded cases (rank-sum test). Table 2 shows the sex distribution in the various centers. The frequency of exclusion was not different for male and female donors, relative to their proportion of the total number (Fisher's exact test, p = 0.38).

The laboratory baseline characteristics are given in Table 3, showing no significant difference between included and excluded procedures (rank-sum test). However, significant differences were found between included cases in the different centers for Hct, Hb, and PLTs ($p < 0.001$), but not for RBCs and WBCs. These differences are considered not to be clinically relevant and may be due to the unequal distribution of age and sex. PLT values were significantly different between male and female donors (p = 0.0247).

TABLE 2. Hematologic data before apheresis of the donors included into the evaluation*

Center	Number of WBCs per nL	Number of RBCs per pL	Hb level (g/dL)	Hct level (%)	Number of PLTs per nL
A	6.4 ± 1.5	4.9 ± 0.4	14.7 ± 1.0	42.7 ± 2.7	241 ± 35
B	6.2 ± 1.4	4.9 ± 0.4	15.0 ± 1.0	45.1 ± 2.9	275 ± 34
C	5.9 ± 1.4	NA	NA	43.0 ± 3.1	253 ± 40
D	5.8 ± 1.2	4.8 ± 0.3	14.6 ± 0.8	41.7 ± 2.2	249 ± 42
E	5.8 ± 1.4	4.9 ± 0.4	14.7 ± 1.1	43.1 ± 2.9	248 ± 38
Cumulative mean	5.9 ± 1.4	4.9 ± 0.4	14.7 ± 1.1	42.9 ± 2.9	251 ± 39

* Data are presented as mean ± SD.

Separations

The blood volume processed, ACD consumption, and donation time were significantly different for single- and double-dose SDPs (Table 3). The study protocol intentionally left full freedom to participating centers to use their apheresis equipment according to their center's existing routines to reflect a broad range of routine operating conditions. Considering the mean values, a good correlation between target and measured volume was reached. The mean volumes were 276 (target) and 266 (measured volume) for single-dose SDPs and 434 (target) and 436 (measured volume) for double-dose SDPs.

PLT concentrates

The absolute yield of PLTs was significantly ($p < 0.05$) lower for single-dose SDPs ($3.11 \times 10^{11} \pm 0.40 \times 10^{11}$) compared to double-dose SDPs ($5.29 \times 10^{11} \pm 0.93 \times 10^{11}$). It should be mentioned that the centers used different adjusted target PLT yields for double-dose SDPs: Centers A and B, 5.5×10^{11}; Center C, 4.3×10^{11}; and Center E, 5.8×10^{11}. For single-dose SDPs, the collection efficiency was 53.7 ± 5.8 percent, and for double-dose SDPs, 58.3 ± 6.2 percent (Fig. 3), respectively. The difference between the collection efficiency of single- and double-dose SDPs was highly significant ($p < 0.001$). The WBC contamination per unit amounts to a mean of $0.11 \times 10^6 \pm 0.20 \times 10^6$ in a single-dose SDP and $0.12 \times 10^6 \pm 0.22 \times 10^6$ in a double-dose SDP ($p > 0.05$). Only in 3 of 441 SDPs was a WBC contamination of more than 1×10^6 per unit observed. The numbers of WBCs in these three products were 1.4×10^6, 1.7×10^6, and 3.0×10^6, respectively. There were no reasons—such as centrifuge stops during the apheresis procedure—found for these elevated WBC counts. The machine does not give a warning to the operator when there is a high WBC contamination in the product. The average RBC contamination was $10.80 \times 10^6 \pm 11.89 \times 10^6$ per unit of single-dose SDP and $7.51 \times 10^6 \pm 13.35 \times 10^6$ per unit of double-dose SDP. Regarding RBC contamination, there was a significant but not relevant difference between single- and double-dose SDPs. There were no SDPs with more than 1×10^8 RBCs per unit.

Donor safety

No severe complications occurred during and after the procedure. A few cases of mild citrate reactions were observed that were treated with oral calcium supplementation.

Counting studies

The data of the two counting studies are shown in Table 4. PLT values were similar as were the numbers of RBCs and WBCs in the whole-blood sample. Dilution of the SDP samples resulted in only little variation of the PLT counts. PLT values in Center A showed a tendency toward lower values. Very low WBC and RBC counts in the SDPs showed considerable deviation from the mean. If the results of each sample were set to unity (to the mean of all centers), most counts were very close to the mean, for example, near to the optimal value 1 (Table 5). There were no significant trends allowing adjustment. No mailing effect was found in the reference center (data not shown).

TABLE 3. Results of single- and double-dose SDPs*

	Single-dose SDPs (n = 342)	Double-dose SDPs (n = 99)
Blood volume processed (mL)	2826 ± 409	3943 ± 639
ACD consumption (mL)	369 ± 63	524 ± 79
Donation time (min)	55 ± 11	71 ± 13
Product volume (mL)	266 ± 26	436 ± 39
PLT yield ($\times 10^{11}$)	3.11 ± 0.93	5.29 ± 0.40
Number of RBCs ($\times 10^6$/unit)	10.94 ± 12.04	12.67 ± 23.68
Number WBCs ($\times 10^6$/unit)	0.11 ± 0.20	0.12 ± 0.22

* Data are presented as mean ± SD.

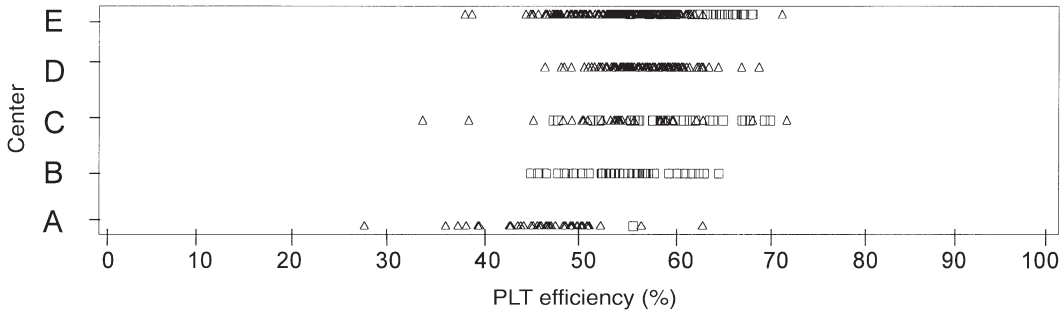

Fig. 3. PLT collection efficiency of 342 single-dose (△) and 99 double-dose (□) SDPs in the five participating centers.

TABLE 4. Results of the two multicenter counting studies*

		Sample 1 (SDP)					Sample 2 (SDP)					Sample 3 (whole blood)			
		Number of RBCs	Number of WBCs	Number of PLTs per nL			Number of RBCs	Number of WBCs	Number of PLTs per nL			Hct level	Number of RBCs	Number of WBCs	Number of PLTs
Center	Study	per μL	per μL	1 in 1	1 in 2	1 in 4	per μL	per μL	1 in 1	1 in 2	1 in 4	(%)	per pL	per nL	per nL
A	1	NA	0.05	948	948	948	25	11.6	909	930	960	45.4	5.25	4.6	202
	2	12.5	0.1	1027	1094	1084	2437	3.7	903	862	908	48.3	5.8	5.0	183
B	1	0	0.22	1209	1224	1244	100	4.3	1181	1226	1208	46.2	5.15	4.8	198
	2	7.05	1.0	1191	952	1360	3200	0.3	1086	988	1100	52.5	6.00	5.2	195
C	1	0	0.5	1214	1190	1164	50	8.5	1214	1194	1124	NA	5.29	4.3	200
	2	125	0.5	1279	1288	1292	3887	5.0	1067	1066	1116	52.3	5.92	4.87	209
D	1	0	0.11	1061	1052	1088	100	8.35	1052	1066	1080	44.7	5.06	4.52	221
	2	25	1.27	1113	1140	1124	2775	7.84	968	1000	988	49.0	5.80	4.25	196
E	1	0	0.1	1192	1144	1216	100	10.5	1174	1174	1176	47.5	5.24	4.6	212
	2	0	0.4	1334	NA	NA	2700	6.0	1123	NA	NA	49.7	5.68	4.7	192

* Two samples of SDPs (Sample 2 spiked with WBCs) and one whole-blood sample were shipped and analyzed. PLTs in the SDPs were counted undiluted (1 in 1) and diluted 1 in 2 and 1 in 4.

TABLE 5. Comparison of the two counting studies for three undiluted samples*

	Ring Study 1			Ring Study 2		
Center	Sample 1	Sample 2	Sample 3	Sample 1	Sample 2	Sample 3
A	0.834	0.807	0.977	0.855	0.875	0.942
B	1.063	1.049	0.958	0.991	1.053	1.004
C	1.067	1.078	0.968	1.065	1.034	1.076
D	0.933	0.934	1.069	0.926	0.938	1.009
E	1.048	1.043	1.026	1.110	1.089	0.986

* Number of PLTs per μL after setting to unity (to the mean of all centers).

DISCUSSION

The new COM.TEC cell separator is an improved version of the Fresenius AS.TEC 204 cell separator. It is less noisy and offers a simplified, more user-friendly menu. An optimized menu algorithm allows a better customizing of procedure (especially anticoagulation) and product. Donor's draw and return flow rates are automatically adjusted to the blood volume calculated by height and body weight. Donor's Hct and PLT values before donation are entered into the menu algorithm, ensuring the collection of a predicted PLT yield. Furthermore, the device makes it possible to additionally collect a plasma unit, which is particularly of interest for centers performing multicomponent donations.

The aim of the present multicenter study was to evaluate the machine's suitability to collect WBC-reduced single- and double-dose SDPs. The results of this multicenter study show that there was only a small deviation of the predicted from the real PLT yield of –2.8 ± 12.0 percent for single-dose and –1.8 ± 9.5 percent for double-dose SDPs, respectively. The collection efficiency of the COM.TEC was higher than with the AS.TEC 204[5,7,9] and AS 104[23,24] cell separators (both from Fresenius), showing the improved potential of the new machine. The collection efficiency for double-dose SDPs was somewhat higher in our study than in a French study (52.4 ± 7.3%) with the COM.TEC blood cell separator.[25] The collection efficiency of 53.7 ± 5.8 percent for single-dose SDPs and of 58.2 ± 6.2 percent for double-dose SDPs is comparable to the results reported of other cell separators (such as Spectra, Cobe, Lakewood, CO; and Amicus, Baxter-Fenwal, Deerfield, IL).[3,6]

Single-dose SDPs could be collected in less than 1 hour, resulting in more donor convenience and in an improved productivity of the apheresis unit. The high number of male donors in our study may have influenced the donation time, and it may take more time to collect SDPs in females with lower blood flow rates. Furthermore, the different PLT baseline values of the male and female donors must be considered when analyzing the results. The PLT yield of the double-dose SDPs was similar to the PLT yield obtained with the Amicus[4-7] and Spectra[3] cell separators. These products can be split in Germany, because the minimal requested PLT dose per unit is 2.0×10^{11}. The splitting of SDPs reduces costs and minimizes donor exposure of the recipients when the two doses of the double-dose SDP are transfused to the same patient on consecutive days.

WBC-reduced SDPs can be collected with the COM.TEC during plateletpheresis without filtration. This is achieved by a new separation chamber that is shaped like continuous spirals. Therefore, PLT loss and/or activation by filtration is avoided. The use of WBC-reduced blood components decreases the risk of alloimmunization,[14,15] generation of cytokines during storage,[16-18] and

transmission of CMV.[19-22] The collected SDPs fulfilled the requirements for WBC-reduced blood components as stated by US, European, and German regulations.[10,26,27] Only three SDPs showed a WBC contamination slightly beyond 10^6 still complying with the German and European guidelines, requiring 90 percent of the units to contain less than 1×10^6.[10,27] With the COM.TEC, WBC contamination of SDPs of less than 1×10^6 can be achieved with a confidence of 99.9 to 98.1 percent. The RBC barrier of the separation avoids a spillover of RBCs during the separation process, resulting also in low RBC contamination of the SDPs. Therefore, all SDPs showed numbers of RBCs of less than 1×10^8, meeting German standards.[10]

Multicenter studies on cell separators give valid data only if the cell counting methods provide comparable results. This must be demonstrated by counting studies. The two counting studies that were part of the presented multicenter study showed only little variation of the PLT counts between the participating centers. The differences were due to the different cell counters that were used in the participating centers.[28] The rather high variation for RBCs and WBCs in samples with very low cell contamination is not surprising.

There were several technical failures during separation procedures with the COM.TEC as a result of software errors, which required exclusion of the results. This exclusion rate was similar to the 6 percent rate of technical problems reported in a study about one of the first software versions of the AS 104 blood cell separator.[13] It is a well-known fact that prototype software shows a high rate of technical failures when they are under routine use. Meanwhile, a new software version, which addresses these failures, has been released. Besides problems with the venipuncture- and anticoagulant-induced side effects, no adverse donor reactions were observed. Because of the low extracorporeal volume of 180 mL, no circulatory side effects occurred.

In summary, the COM.TEC cell separator allows safe and efficient collection of WBC-reduced SDPs. The WBC contamination of the SDPs complies well with current US and European standards.

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