Hemostatic Efficacy of Platelet Components Treated with Amotosalen-UVA Pathogen Inactivation and Stored for 5 and 7 Days Prior To Transfusion

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Background

In some countries, bacterial contamination of platelet components (PC) limits PC storage to 4-5 days to reduce the risk of transfusion-related sepsis (TRS). Bacterial detection is only partially effective in preventing release of contaminated PC. Pathogen inactivation (PI) of bacteria facilitates storage of PC to 5 and 7 days limiting TRS risk, reducing PC wastage, and increasing PC inventory. The hemostatic efficacy of 5 and 7 day old PC has not been extensively characterized.

Aims

- **To compare the therapeutic efficacy of platelet concentrates (PC) stored specifically for 5 days to those stored for 6 or 7 days.**
- **To compare the therapeutic efficacy of conventional platelet components and components treated with pathogen inactivation (Amotosalen-UVA).**

Methods

Data were analyzed from 3 randomized controlled clinical trials:

(1) Phase 3 clinical study with buffy coat platelets conducted in Europe (EuroSPRITE trial).

(2) Phase 3 clinical study with apheresis platelets conducted in the US (SPRINT trial).

(3) Clinical study with apheresis or buffy coat platelets stored for at least 6 and not more than 7 days prior to transfusion conducted in Europe (TESSI trial).

Data related to the first transfusion for each patient of 5-day-old PC were extracted from the EuroSPRITE and SPRINT clinical trial databases and compared with the data from the TESSI trial in which only a single PC stored for more than 5 days was transfused. Comparisons across the three studies for both INTERCEPT (Amotosalen-UVA) and Control PC for all outcome measures considered relevant to therapeutic efficacy included: CI and CCI at 1-hour and 24-hours post-transfusion, time to next platelet transfusion, red cell transfusion requirement and hemorrhagic adverse events (AE) within 24 hours of transfusion.

Post hoc comparisons across different studies, especially when focused on a selected subset of transfusions provide a qualitative assessment of transfusion effectiveness despite the limitation that these comparisons lack the prospective design to support definitive statistical analyses. P-values for comparisons between INTERCEPT and Control PC within a study are provided as reference. Comparisons across studies were not statistically evaluated due to differences in the design and intention of each clinical trial, therefore only qualitative comparisons were made.

Results

All transfusions of 6 and 7 day old PC for the TESSI study were analysed, while for SPRINT and EuroSPRITE only the first transfusion of a 5-day old PC was represented.

There is mechanical loss of platelets during INTERCEPT processing. In the SPRINT study, if platelet units were below the targeted minimum transfusion dose, these units were still transfused to maintain patients within their treatment assignment. As a result, mean platelet dose was significantly lower in the INTERCEPT arm (3.5×10^{11}) in comparison to the Control arm (3.9×10^{11}). In addition, a substantial proportion (20%) of INTERCEPT PC contained $<3.0 \times 10^{11}$ platelets [1, 3]. A similar dose differential was present in the EuroSPRITE study (**Table 1**). With dosage managed more actively and consistently during PC manufacturing, mean dose was identical between INTERCEPT and Reference in the TESSI study, and fewer low dose transfusions were given during the TESSI study since only a single PC was required in order to remain on protocol (**Table 1**).

The 1 hour CI and CCI were compared across the 3 clinical studies of interest (EuroSPRITE, SPRINT, and TESSI) for 5 day old and 6/7 day old conventional and pathogen inactivated PC (**Table 2**). EuroSPRITE was conducted only with whole blood derived buffy coat PC, SPRINT was conducted solely with apheresis PC, and TESSI utilized a mixture of whole blood derived buffy coat PC and apheresis PC. Across the studies, CI was generally similar but somewhat lower for INTERCEPT PC. CCI, consistent with product age, was somewhat lower for 7-day old PC in the TESSI study (both INTERCEPT and Control groups), but all CCI values were in a range generally considered to provide acceptable hemostasis: CCI >5000 at 1 hour post-transfusion [2] (**Table 2**).

The CI and CCI at 24 hours post-transfusion were also compared across the 3 clinical studies (**Table 3**). Count increments measured at 24 hours post-transfusion are more affected by confounding clinical factors than the 1 hour CI and CCI, and, thus direct measures such as post-transfusion hemorrhage in the first 24 hours, use of RBC components to support bleeding, and time to the next PC transfusion are more relevant indices than the 24 hour CI and CCI. Across the studies, 24h CI was generally similar. CCI, consistent with product age, was somewhat lower for 7 day old PC in the TESSI study for both INTERCEPT and Control arms (**Table 3**).

The time to next transfusion summary statistics demonstrate that the time to the next PC transfusion remained reasonably constant at approximately 2 days across all 3 clinical studies (**Table 4**). A difference between INTERCEPT and Control for this parameter was present in the SPRINT trial and was likely due to the lower mean PC dose transfused and the increased proportion of PC doses $< 3.0 \times 10^{11}$ in the INTERCEPT group [3]. Such a dose-dependent difference in transfusion interval is consistent with findings from the recently completed Platelet Dosage (PLADO) study [2]. In the TESSI study, with well controlled PC doses, no difference in time to next transfusion was found.

Use of red cell components given within 24 hours of a study PC transfusion was compared across the 3 clinical trials (**Table 5**). The most striking and reassuring finding is that, across all 3 studies, approximately 75-80% of subjects received no red cell components in the 24 hour period after a 5 or 7 day-old PC. A small proportion of subjects were transfused with either 1 or 2 red cell units. A pattern of more single unit red cell transfusions in the earlier trials (SPRINT and EuroSPRITE) was observed in comparison to the later trial (TESSI). This observed decline in single unit transfusions may represent the evolution of better, more stringent transfusion practice which reflects use of a lower hemoglobin threshold for RBC transfusion, and more transfusions consisting of 2 RBC units [4] (**Table 5**).

The number of hemorrhagic AEs stratified by platelet product age and AE intensity grade for both INTERCEPT and Control groups were compared (**Table 6**).

Overall, 516 subjects received a 5-day old platelet component (266 INTERCEPT, 250 Control) and 211 patients received a 6/7-day old platelet component (106 INTERCEPT, 105 Control). Of the 516 patients who received a 5-day old platelet component, 42% experienced at least one hemorrhagic AE in the 24 hours following transfusion. Of the 211 patients who received a 6/7-day old platelet component, 17% experienced at least one hemorrhagic AE (16 INTERCEPT, 20 Control). The majority of hemorrhagic AEs were mild in intensity. Across the studies, the rates of hemorrhagic AEs were generally similar whether the PC transfused was 5-days old or 6/ 7-days old (**Table 6**).

Conclusions

- **5 and 7 day-old PI-PC supported hemostasis, measured by bleeding and RBC use, comparable to Control-PC.**
- **CI and CCI did not predict, or correlate with hemostatic efficacy, consistent with data from the PLADO study (N Eng J Med 2010; 362:600).**
- **When dose was controlled, the interval to the next PC transfusion was similar for PI and Control-PC.**
- **A synthesis of bleeding assessments, RBC use, and transfusion interval provided evidence that 5 and 7 day-old PI-PC were therapeutically effective with the added benefit of broad spectrum pathogen inactivation.**

Table 1: Platelet Unit Dose (10^{11})Comparing 5-Day Old PC with 6/7-Day Old PC

	EuroSPRITE[a]		SPRINT[b]		TESSI[b]	
	INTERCEPT	Control	INTERCEPT	Control	INTERCEPT	Control
Patients (N)	35	27	231	223	105	106
Mean Dose (SD)	3.5 (0.99)	4.1 (0.98)	3.5 (0.70)	3.9 (0.85)	4.2 (0.67)	4.2 (0.67)
Median Dose	3.2	4.0	3.5	3.9	4.1	4.1

Note: Wilcoxon rank-sum test used to compare platelet dose distributions between treatment groups within each study.
EuroSPRITE: p = 0.002; SPRINT: p < 0.0001; TESSI: p = 0.966

Table 2: 1-hr Count Increment (CI) and Corrected Count Increment (CCI) Comparison for 5 and 6/7 Day Old PC

	EuroSPRITE[a]		SPRINT[b]		TESSI[b]	
	INTERCEPT	Control	INTERCEPT	Control	INTERCEPT	Control
Patients (N)	33	26	218	201	103	104
Mean 1-hr CI (SD)[c]	21.4 (13.75)	27.3 (14.03)	18.9 (14.33)	30.3 (19.75)	19.2 (13.42)	22.8 (18.29)
Median 1-hr CI[c]	19.0	27.5	16.0	27.0	17.0	20.0
Mean 1-hr CCI (SD)[d]	11.7 (6.67)	12.9 (6.35)	10.1 (7.45)	14.1 (8.33)	8.1 (5.37)	9.7 (7.10)
Median 1-hr CCI[d]	11.6	12.2	9.2	13.4	7.3	8.8

Note: Wilcoxon rank-sum test used to compare 1-hr CI and CCI distributions between treatment groups within each study.
EuroSPRITE: 1-hr CI (p=0.062); 1-hr CCI (p=0.426); SPRINT: 1-hr CI (p<0.0001); 1-hr CCI (p<0.0001)
TESSI: 1-hr CI (p=0.123); 1-hr CCI (p=0.063)

Table 3: 24-hr Count Increment (CI) and Corrected Count Increment (CCI) Comparison for 5 and 6/7 Day Old PC

	EuroSPRITE[a]		SPRINT[b]		TESSI[b]	
	INTERCEPT	Control	INTERCEPT	Control	INTERCEPT	Control
Patients (N)	32	25	193	195	102	105
Mean 24-hr CI (SD)[c]	12.8 (14.90)	17.8 (12.95)	12.5 (14.23)	19.3 (16.70)	11.6 (10.03)	14.6 (11.95)
Median 24-hr CI[c]	11.5	16.0	9.0	16.0	10.0	14.0
Mean 24-hr CCI (SD)[d]	6.8 (8.19)	8.4 (5.89)	6.5 (7.01)	8.9 (7.03)	4.9 (4.14)	6.3 (5.15)
Median 24-hr CCI[d]	6.3	7.3	5.0	7.7	4.7	6.1

Note: Wilcoxon rank-sum test used to compare 24-hr CI and CCI distributions between treatment groups within each study.
EuroSPRITE: 24-hr CI (p=0.245); 24-hr CCI (p=0.351); SPRINT: 24-hr CI (p<0.0001); 24-hr CCI (p<0.001).
TESSI: 24-hr CI (p=0.050); 24-hr CCI (p=0.019).

a. EuroSPRITE and SPRINT: initial 5-day stored platelet transfusion exposure (intent to treat population).
b. TESSI: initial 6 or 7-day stored platelet transfusion exposure (intent to treat population).
c. $\times 10^9$/L
d. $\times 10^6$
e. Platelet independence achieved when time between transfusions is at least 7 days.
f. Censored values were ignored when calculating these summary statistics.
g. Percentage of total events.

Table 4: Time to Next Platelet Transfusion Comparison for 5 and 6/7 Day Old PC[e]

	EuroSPRITE[a]		SPRINT[b]		TESSI[b]	
	INTERCEPT	Control	INTERCEPT	Control	INTERCEPT	Control
Patients (N)[f]	34	27	191	191	87	87
Mean (SD)[f]	2.5 (1.28)	2.8 (1.27)	1.6 (1.08)	2.2 (1.26)	2.0 (1.31)	2.0 (1.20)
Median[f]	2.5	3.0	1.2	2.0	1.8	1.9

Note: Log-rank test used to compare time to next platelet transfusion distributions between treatment groups within each study.
EuroSPRITE: p = 0.750 SPRINT: p < 0.0001 TESSI: p = 0.717

Table 5: RBC Units Transfused Within 24 Hours of Study Transfusion for First Transfusion of 5-Day Old PC and 6/7-Day Old PC

Patients (N) / #RBC Units	EuroSPRITE[a]		SPRINT[b]		TESSI[b]	
	INTERCEPT	Control	INTERCEPT	Control	INTERCEPT	Control
	35	27	231	223	105	106
0	26 (74.3%)	20 (74.1%)	175 (75.8%)	174 (78.0%)	80 (76.2%)	83 (78.3%)
1	7 (20.0%)	5 (18.5%)	37 (16.0%)	35 (15.7%)	3 (2.9%)	1 (0.9%)
2	2 (5.7%)	2 (7.4%)	17 (7.4%)	14 (6.3%)	22 (21.0%)	20 (18.9%)
3	0	0	2 (0.9%)	0	0	1 (0.9%)
6	0	0	0	0	0	1 (0.9%)

Note: Wilcoxon rank-sum test used to compare the distributions of RBC units transfused between treatment groups within each study.
EuroSPRITE: p = 0.963; SPRINT: p = 0.514; TESSI: p = 0.821

Table 6: Frequency Distributions of Patients with Any Hemorrhagic AE Stratified by Study or Platelet Component Age at Time of Transfusion

Patients	EuroSPRITE		SPRINT		TESSI		INTERCEPT		Control	
	INTERCEPT (N=35)	Control (N=27)	INTERCEPT (N=231)	Control (N=223)	INTERCEPT (N=105)	Control (N=106)	5-day (N=266)	6/7-day (N=105)	5-day (N=250)	6/7-day (N=106)
No Hemorrhagic AE	23 (66%)[g]	18 (67%)	124 (54%)	133 (60%)	89 (85%)	86 (81%)	147 (55%)	89 (85%)	151 (60%)	86 (81%)
Mild Hemorrhagic AE (Grade 1)	11 (31%)	8 (30%)	77 (33%)	65 (29%)	10 (10%)	16 (15%)	88 (33%)	10 (10%)	73 (29%)	16 (15%)
Moderate Hemorrhagic AE (Grade 2)	1 (3%)	1 (4%)	16 (7%)	16 (7%)	5 (5%)	3 (3%)	17 (6%)	5 (5%)	17 (7%)	3 (3%)
Severe Hemorrhagic AE (Grade 3 and 4)	0	0	14 (6%)	9 (4%)	1 (1%)	1 (1%)	14 (5%)	1 (1%)	9 (4%)	1 (1%)

Note: For patients with more than one hemorrhagic AE, only the maximum grade is counted. 5-day platelet data were pooled from the EuroSPRITE and SPRINT clinical trials. 6/7-day platelet data were derived from the TESSI clinical trial.

References

1. McCullough, J., D. H. Vesole, et al. Blood 2004:104(5);1534-41; **2.** Slichter, S. J., R. M. Kaufman, et al. N Engl J Med 2010:362;600-613; **3.** Murphy, S., E. Snyder, et al. Transfusion 2006:46;24-33; **4.** Carless, P. A., D. A. Henry, et al. Cochrane Database Syst Rev2010:(10);CD002042.