A comparison of adverse reaction rates for PAS C versus plasma platelet units

Claudia S. Cohn,[1] James Stubbs,[2] Joseph Schwartz,[3] Richard Francis,[3] Cheryl Goss,[4] Melissa Cushing,[4] Beth Shaz,[5] David Mair,[6] Barbara Brantigan,[7] and W. Andrew Heaton[8]

BACKGROUND: Plasma constituents have been implicated in some types of platelet (PLT) transfusion reactions. Leukoreduced apheresis PLTs stored in InterSol have 65% less plasma than apheresis PLTs stored in 100% plasma (PPs). This study compared transfusion reaction rates in InterSol PLTs (PLT additive solution [PAS] C) versus PPs.

STUDY DESIGN AND METHODS: The study design was an open-label, nonrandomized retrospective review. Statistical methods were applied to substantiate noninferiority and superiority of PAS C compared to PP in terms of transfusion reaction rates. Adverse reactions (ARs) were categorized using the Biovigilance Component of the National Healthcare Safety Network. Active surveillance was used to monitor all transfusions, both with ARs and without ARs.

RESULTS: A total of 14,005 transfusions from six study sites were included, with 9845 PP transfusions given to 2202 patients and 4160 PAS C to 1444 patients. A total of 165 ARs were reported. Percentages of transfusions with ARs were 1.37% for PPs, 0.55% for PAS C, and 1.13% overall. The relative risk (RR) for PAS C versus PPs was calculated as 0.403 with an upper confidence limit (UCL) of 0.663. Overall, ARs with the highest incidence were allergic transfusion reactions (ATRs) and febrile nonhemolytic transfusion reactions (FNHTRs), at 0.66 and 0.40% of total transfusions reported, respectively. The relative risks (UCLs) for ATRs and FNHTRs, respectively, were 0.350 (0.686) and 0.336 (0.827).

CONCLUSIONS: PAS C PLTs were statistically superior and noninferior to PPs with respect to the transfusion-related AR rate. PAS C noninferiority and superiority were also demonstrated for ATRs and FNHTRs, separately.

Transfusion reactions to platelets (PLTs) can range from a mild urticarial response to severe, disabling events. Estimates of the rate of transfusion reactions to leukoreduced apheresis PLT concentrates range from approximately 1% to 4%.[1-5] The majority of these are classified as either allergic transfusion reactions (ATRs) or febrile nonhemolytic transfusion reactions (FNHTRs).[3,5,6] While the signs and symptoms for these reactions vary widely, the underlying cause has been

ABBREVIATIONS: AR(s) = adverse reaction(s); ATR(s) = allergic transfusion reaction(s); CEC = clinical events committee; FNHTR(s) = febrile nonhemolytic transfusion reaction(s); NHSN = National Healthcare Safety Network; PAS = platelet additive solution; PP(s) = plasma platelet(s); PTP = posttransfusion purpura; TACO = transfusion-associated circulatory overload; TAD = transfusion-associated dyspnea; UCL(s) = upper confidence limit(s).

From the [1]Department of Laboratory Medicine and Pathology, University of Minnesota Medical School, Minneapolis, Minnesota; the [2]Mayo Clinic, Rochester, Minnesota; the [3]Department of Pathology and Cell Biology, Columbia University Medical Center-New York Presbyterian Hospital, the [4]Department of Pathology and Laboratory Medicine, Weill Cornell Medical Center, and [5]Medical Programs and Services, New York Blood Center, New York, New York; the [6]American Red Cross–North Central Region, St Paul, Minnesota; [7]Fenwal, a Fresenius-Kabi Company, Lake Zurich, Illinois; and [8]Transfusion Service and Donor Services, North Shore University Hospital, Manhasset, New York.

Address reprint requests to: Claudia S. Cohn, MD, PhD, Laboratory Medicine & Pathology, University of Minnesota, MMC 609, 420 Delaware Street SE, Minneapolis, MN 55455; e-mail: cscohn@umn.edu.

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linked to the plasma in which units are stored.[6-8] ATRs, which are the most commonly reported complication of a blood transfusion, are usually Type I hypersensitivity reactions that result from allergens within the donor plasma interacting with preformed immunoglobulin E antibodies in the recipient. FNHTRs associated with PLT transfusions are thought to be due to cytokines, released by white blood cells (WBCs) into the plasma fraction.[9] Thus apheresis PLTs stored with less plasma, such as PLTs stored in a PLT additive solution (PAS), should have lower adverse event rates.

Reducing the plasma in PLT units has been shown to reduce some types of transfusion reactions;[8,10-13] however, conventional techniques such as volume reduction and washing are labor-intensive manipulations that can compromise product quality. Using PLTs stored in PAS is an alternative method for plasma reduction because much of the plasma is replaced by PAS. Studies have shown a reduction in adverse reactions (ARs) when comparing PAS PLTs to plasma-based units.[14-16]

In the United States, InterSol solution (PAS 3, Fenwal, a Fresenius Kabi Company, Lake Zurich, IL) has been approved as an isotonic solution designed to replace 65% of the plasma used in the storage of Amicus-derived leukoreduced apheresis PLTs. When an apheresis PLT unit is stored in PAS 3 (InterSol), it is referred to as a PAS C unit. The reduction in plasma in PAS C units should reduce the frequency of ARs. We have conducted a multicenter, open-label, retrospective study to compare the rate of ARs related to PAS C PLTs to that of conventional plasma PLT (PP) units.

MATERIALS AND METHODS

Study design

An open-label, nonrandomized retrospective study was conducted to evaluate the rate of transfusion-related adverse events in recipients of apheresis PLTs in plasma compared to PAS C PLTs. The study protocol was approved by the institutional review board of all participating institutions. Patients were prescribed PLT transfusions per each site's standard practice. All patients receiving a PLT transfusion between January 29, 2012, and September 30, 2012, were transfused with either PAS C or 100% PP units. The patients were not maintained on only one arm of the study and could receive either PAS C or PPs; the type of unit released by the blood bank was based on the inventory at the site at the time the transfusion was ordered. When multiple units were released simultaneously for a patient, there may have been a mix of both kinds of units. The patient's history did not factor into the decision regarding which kind of PLT unit was selected; neither the blood bank staff nor the transfusing physician could specifically select a PAS C versus a PP unit for a specific patient.

Transfusions that led to ARs were reported according to standard procedures at each site. Active surveillance of transfusion records was employed to identify transfusions which led to ARs, as well as to affirm those which did not produce reactions. All data were collected retrospectively.

Inclusion and exclusion criteria

Patients were prescribed PLT transfusions per the site's standard practice, based on the available inventory at each site at the time the PLT unit was ordered. Only full-dose, apheresis PLTs in either 100% plasma or PAS C were included in the study; however, neonates and some pediatric patients received split units based on their weight. When aliquots of units were transfused each aliquot was counted as an individual transfusion event. PLT units given in areas that did not maintain full active surveillance of transfusion reactions were excluded.

Age and sex

Age categories were defined as follows: neonate, 1 to 31 days of age; infant, 1 to 12 months of age; child, 1 to 17 years of age; and adult, 18 years or older. After the original planned analysis, age and sex data were collected and analyzed for informational purposes. This additional information was acquired by chart rereview and supplied in the same blinded manner.

Evaluation of adverse events

Transfusion reactions were reported by clinical personnel according to the standard procedures in place at each study site. In addition, all PLT transfusions were actively monitored for ARs by trained study personnel, using definitions outlined by the Biovigilance Component of the National Healthcare Safety Network (NHSN) System, Hemovigilance Module Surveillance Protocol v1.3.1. An independent clinical events committee (CEC), composed of transfusion medicine experts, adjudicated the reported events in a manner blinded to the type of PLT transfused and to study site. The CEC determined if the criteria outlined in the NHSN Hemovigilance Module Protocol v1.3.1 had been followed. When the CEC needed to resolve a perceived discordance and/or obtain additional information, all deidentified requests and responses were transmitted through the industry sponsor to maintain blinding. Only CEC-adjudicated data were used in the analyses reported herein.

Concurrent transfusions

Concurrent transfusions were defined in the study as sequential PLT units administered within less than 1 hour

and that led to a reaction. Any reactions associated with concurrent transfusions that included both PAS C and PPs would be associated with only one product, based on the decision of the site investigator. Although this eventuality was anticipated, no concurrent transfusions occurred during the study.

PAS C PLT unit preparation

The PAS 3 solution (InterSol) is a third-generation product composed of di- and monobasic sodium phosphate, sodium citrate, sodium acetate, and sodium chloride. After a PLT unit is collected with the cell separator software (Amicus, Version 3.2, Fenwal, Inc.) and suspended in the PAS 3 solution, it is considered to be a PAS C unit. PAS C units were produced as follows: After PLT collection, the operator manually connected the PAS 3 solution to the appropriate connector line on the Amicus kit. The PAS 3 solution was added automatically during the PLT resuspension. The process replaces 65% of the plasma with PAS 3 solution. The resuspended PLTs remained at rest for a minimum of 10 minutes. PLTs stored in PAS 3 solution are referred to as PAS C PLT units.

Both PAS C and PP PLTs were collected at blood collection centers from donors at low risk for transfusion-related acute lung injury (TRALI), including a predominantly male population, nulliparous females, and females who had negative screening tests for HLA antibodies. All standard full-dose PLT units were supplied directly to participating sites through standard ordering procedures.

Determination of sample size

The two-sample relative risk statistic with the Poisson assumption was used to evaluate differences in AR rates. A reaction rate was defined as the number of transfusions associated with a reaction divided by the total number of transfusions, for either PAS C or PP and overall. Available historical data from a site participating in the CDC Hemovigilance System reported an AR rate of 0.0056. This was used to project a minimum sample size of 11,626 transfusions required to demonstrate that the transfusion-related AR rate in the PAS C group was less than double the rate in the PP group with 97.5% confidence (one-sided) and at least 80% power and an observed relative risk hypothesized as 1.0.

Statistical analysis

To evaluate the difference in transfusion-based AR rates, relative risk and a likelihood ratio-based two-sided 95% confidence interval (CI) were estimated using a modified Poisson regression with group as a fixed effect and patient as a repeated effect that utilized an independent covariance matrix and the logarithm link function. A noninferiority margin of 100% (i.e., relative risk, 2.0) was used, which coincides with a "less than double" hypothesis. The difference in patient-based AR rates was described by calculating a two-sided Wald 95% CI for the difference in proportions. Analysis was performed using the computer software (procedure GENMOD in SAS, Version 9.1.3, SAS Institute, Cary, NC).

Additional hypothesis testing

If the primary study objective was statistically substantiated, then it was determined if the transfusion-related AR rate in the PAS C group was statistically less than (superior to) the PP group. If the 97.5% upper confidence limit (UCL) was less than 1.0, a claim of superiority could be statistically substantiated. A Type I error multiplicity adjustment was not required for testing superiority in a significant noninferiority trial.

RESULTS

Patient population

Data collection dates varied slightly by institution, but were all within the time period from January 2012 to the end of September 2012. In this interval, 14,005 PLT transfusions were administered at six study sites (see Table 1).

TABLE 1. Number of transfusions and patients by deidentified site*

	PAS C		Plasma		Total	
Deidentified sites	All transfusions†	All patients transfused‡	All transfusions†	All patients transfused‡	All transfusions†	All patients transfused‡
A	1340 (32.21)	240 (16.62)	3125 (31.74)	315 (14.31)	4,465 (31.88)	350 (13.44)
B	1002 (24.09)	446 (30.89)	3053 (31.01)	777 (35.29)	4,055 (28.95)	882 (33.86)
C	319 (7.67)	135 (9.35)	719 (7.30)	222 (10.08)	1,038 (7.41)	273 (10.48)
D	420 (10.10)	167 (11.57)	639 (6.49)	215 (9.76)	1,059 (7.56)	283 (10.86)
E	444 (10.67)	218 (15.10)	933 (9.48)	333 (15.12)	1,377 (9.83)	421 (16.16)
F	635 (15.26)	238 (16.48)	1376 (13.98)	340 (15.44)	2,011 (14.36)	396 (15.20)
Overall	4160 (100.00)	1444 (100.00)	9845 (100.00)	2202 (100.00)	14,005 (100.00)	2605 (100.00)

* Data are reported as number (%).
† Percentage = number of transfusions by site/total number of transfusions overall.
‡ Percentage = number of transfused patients by site/total number of transfused patients overall.

TABLE 2. Sex and age of patients transfused*

Sex	
Female	1055 (40.5)
Male	1550 (59.5)
Overall	2605 (100.0)
Age	
Adult	2341 (89.9)
Child	172 (6.6)
Infant	45 (1.7)
Newborn	47 (1.8)
Overall	2605 (100.0)

* Data are reported as number (%).

TABLE 3. Summary of the relative risk of transfusion-related ARs (all transfusions)

PAS C (N = 4160)*	Plasma (N = 9845)*	Relative risk† (PAS C/Plasma)	UCL†
23 (0.55)	135 (1.37)	0.403	0.663

* Data are reported as number (%). Percentage = number of transfusions related to a reaction/total number of transfusions.
† From a modified Poisson regression with effect treatment and repeated effect patient utilizing an independent covariance matrix and the logarithm link function.
N = total number of transfusions; n = number of transfusions that led to any AR.

These transfusions consisted of 9845 PP units transfused to 2202 patients and 4160 PAS C units transfused to 1444 patients. Patients ranged from 1 day old to 102 years of age, and there was a slight male predominance (see Table 2).

Transfusion reaction frequencies

A total of 167 ARs were reported by the sites; two were removed and four were changed after the CEC reviewed the data. The removed reactions were from the plasma arm and included reports of posttransfusion purpura (PTP) and a FNHTR. The signs and symptoms of PTP were present before the transfusion, and the FNHTR occurred in an already febrile patient with a urinary tract infection. The CEC reviewed additional blinded information provided by the sites in each case above and ruled that these were due to underlying conditions and not related to the PLT transfusions. The four changed diagnoses included two from each arm of the study: for PP there was an ATR changed to "Other: Erythema" and a transfusion-associated dyspnea (TAD), which was changed to transfusion-associated circulatory overload (TACO). For the PAS C–related reactions two diagnoses of TAD were changed to TACO, both for the same patient 3 days apart. The final number of CEC-adjudicated reactions was 165, 23 for PAS C and 142 for PPs. Seven PP transfusions caused two simultaneous reactions (e.g., signs and symptoms of ATR and FNHTR reported after 1 unit transfused). Therefore, the total number of transfusions that led to reactions in both arms was 158.

The overall percentage of transfusions associated with a reaction was 1.13% (158/14,005). The percentage of transfusions associated with PAS C PLTs was 0.55% (23/4160), compared to 1.37% (135/9845) for PPs (see Table 3). For ARs, the relative risk for PAS C PLTs in relation to plasma units was 0.403, with a UCL of 0.663. Since the UCL was less than 2.0, the noninferiority of PAS C to PPs was statistically substantiated. In addition, since the primary null hypothesis was rejected, and the 97.5% UCL was less than 1.0, the statistical superiority of PAS C to PPs with respect to transfusion-related AR rate was demonstrated.

Transfusion reaction categories

The classification of transfusion reactions is shown in Tables 4A and 4B. The most frequently reported reaction for both arms of the study was allergic (n = 93), with a PAS C transfusion reaction rate of 0.29% (12/4160) versus a reaction rate of 0.82% (81/9845) for PP transfusions. When ATRs were analyzed based on all patients transfused, the percentage of patients who experienced a reaction was 12 of 1444 (0.83%) in the PAS C arm compared to 69 of 2202 patients (3.13%) in the PP arm. The relative risk of an ATR for PAS C in relation to PPs was 0.350 (97.5%; UCL, 0.686). Thus PAS C PLTs were statistically less likely to cause a reaction.

The second most frequent reaction reported was FNHTR (n = 56). The PAS C and PP transfusion reaction rates for FNHTRs were 0.17 and 0.50% of total product-specific transfusions, respectively. When compared to all patients transfused, the percentage of patients who experienced a reaction was seven of 1444 (0.48%) for PAS C versus 42 of 2202 (1.91%) for PPs. The relative risk of an FNHTR for PAS C in relation to PPs was 0.336 (97.5%; UCL, 0.827). The relative risk and UCL values for ATRs and FNHTRs both satisfied the requirements for proving statistical noninferiority and superiority of PAS C PLTs in relation to PPs.

The rate of all other transfusion reactions was either smaller for PAS C versus PP transfusions or equal in both arms (see Table 4A). These numbers, however, were too small to achieve significance.

Repeat transfusion reaction

A repeat reaction was defined as the same category of reaction occurring in the same patient in response to a different PLT transfusion. The 23 ARs to PAS C occurred in 22 patients, while the 142 PP reactions happened in 115 patients. Repeat reactions were most frequently ATRs, and

TABLE 4A. Type of transfusion reactions: number of PLT transfusions causing ARs*

	PAS C (N = 4160)		Plasma (N = 9845)		Total (N = 14,005)	
AR category	Trx†	Rxn	Trx†	Rxn	Trx†	Rxn
Allergic reaction, including anaphylaxis	12 (0.29)	12	81 (0.82)	81	93 (0.66)	93
Acute hemolytic transfusion reaction	0 (0.00)	0	0 (0.00)	0	0 (0.00)	0
Delayed hemolytic transfusion reaction	0 (0.00)	0	0 (0.00)	0	0 (0.00)	0
Delayed serologic transfusion reaction	0 (0.00)	0	0 (0.00)	0	0 (0.00)	0
FNHTR	7 (0.17)	7	49 (0.50)	49	56 (0.40)	56
Hypotensive transfusion reaction	1 (0.02)	1	2 (0.02)	2	3 (0.02)	3
Infection	0 (0.00)	0	0 (0.00)	0	0 (0.00)	0
PTP	0 (0.00)	0	0 (0.00)	0	0 (0.00)	0
TACO	2 (0.05)	2	6 (0.06)	6	8 (0.06)	8
TAD	0 (0.00)	0	2 (0.02)	2	2 (0.01)	2
Transfusion-associated graft-vs.-host disease	0 (0.00)	0	0 (0.00)	0	0 (0.00)	0
TRALI	0 (0.00)	0	0 (0.00)	0	0 (0.00)	0
Other						
Chest tightness or anxiety	0 (0.00)	0	1 (0.01)	1	1 (0.01)	1
Erythema	0 (0.00)	0	1 (0.01)	1	1 (0.01)	1
Nausea, dizziness	1 (0.02)	1	0 (0.00)	0	1 (0.01)	1
Overall‡	23 (0.55)	23	135 (1.37)	142	158 (1.13)	165

* All reactions were adjudicated by the CEC.
† Data are reported as number (%). Percentage = number of transfusions related to a reaction/total number of transfusions.
‡ Some transfusions led to more than one type of reaction; hence the overall transfusion values for "n" pertain only to unique reactive transfusions overall.
N = total number of transfusions; n = the number of transfusions that led to a reaction or the number of reactions; Rxn = reactions; Trx = transfusions.

TABLE 4B. Type of transfusion reactions: number of patients with ARs*

	PAS C (N = 1444)		Plasma (N = 2202)		Total (N = 2605)	
AR category	Patients†	Rxn	Patients†	Rxn	Patients†	Rxn
Allergic reaction, including anaphylaxis	12 (0.83)	12	69 (3.13)	81	78 (2.99)	93
Acute hemolytic transfusion reaction	0 (0.00)	0	0 (0.00)	0	0 (0.00)	0
Delayed hemolytic transfusion reaction	0 (0.00)	0	0 (0.00)	0	0 (0.00)	0
Delayed serologic transfusion reaction	0 (0.00)	0	0 (0.00)	0	0 (0.00)	0
FNHTR	7 (0.48)	7	42 (1.91)	49	48 (1.84)	56
Hypotensive transfusion reaction	1 (0.07)	1	2 (0.09)	2	3 (0.12)	3
Infection	0 (0.00)	0	0 (0.00)	0	0 (0.00)	0
PTP	0 (0.00)	0	0 (0.00)	0	0 (0.00)	0
TACO	1 (0.07)	2	6 (0.27)	6	7 (0.27)	8
TAD	0 (0.00)	0	2 (0.09)	2	2 (0.08)	2
Transfusion-associated graft-vs.-host disease	0 (0.00)	0	0 (0.00)	0	0 (0.00)	0
TRALI	0 (0.00)	0	0 (0.00)	0	0 (0.00)	0
Unknown pathophysiology	0 (0.00)	0	0 (0.00)	0	0 (0.00)	0
Other						
Chest tightness or anxiety	0 (0.00)	0	1 (0.05)	1	1 (0.04)	1
Erythema	0 (0.00)	0	1 (0.05)	1	1 (0.04)	1
Nausea, dizziness	1 (0.07)	1	0 (0.00)	0	1 (0.04)	1
Overall‡	22 (1.52)	23	115 (5.22)	142	127 (4.88)	165

* All reactions were adjudicated by the CEC.
† Data are reported as number (%). Percentage = number of patients who experienced a reaction/total number of patients.
‡ Some patients experienced more than one type of reaction; hence the overall patient values for "n" pertain only to unique patients who experienced reactions overall.
N = total number of patients; n = the number of patients who experienced a reaction or the number of reactions; Rxn = reactions.

these were only seen with PP units (81 reactions in 69 patients). In addition, there were 49 FNHTRs in 42 patients receiving PP transfusions. The single patient who had a repeat reaction to PAS C experienced TACO from two separate PAS C transfusions 3 days apart.

Influence of sex and age on transfusion reactions

An analysis of reactions in the pediatric population is in Table 5. A total of 425 transfusions were given to neonates and infants (128 PAS C; 297 PP); however, no ARs were reported in these age groups. For children older than 1

TABLE 5. Transfusion reaction rates for pediatric patients*

	PAS C	Plasma	Overall	p value†
Number of transfusions (T)	735	2001	2736	
Number of transfusions associated with a reaction (R)	1	19	20	
Reaction rate‡	0.001	0.009	0.007	0.0262

* Pediatric patients = less than 18 years of age.
† From a modified Poisson regression with a compound symmetry covariance matrix and the logarithm link function to test for differences in reaction rates by product.
‡ Reaction rate = R/T.

TABLE 6. Summary of transfusion-related ARs by severity (all transfusions)

	PAS C		Plasma		Total	
Severity	Trx*	Rxn	Trx*	Rxn	Trx*	Rxn
Nonsevere	21 (91.30)	21	130 (96.30)	137	151 (95.57)	158
Severe	2 (8.70)	2	5 (3.70)	5	7 (4.43)	7
Life-threatening	0 (0.00)	0	0 (0.00)	0	0 (0.00)	0
Death	0 (0.00)	0	0 (0.00)	0	0 (0.00)	0

* Data are reported as number (%). Transfusions associated with one or more ARs are counted under the most severe and only once within a given cell. Percentage = number of transfusions by reaction severity/total number of reactive transfusions overall.
Rxn = reactions; Trx = transfusions.

year, there were 19 reactions resulting from 2001 PP transfusions (0.9%) in 150 patients. In contrast, there was a single reaction from 735 PAS C transfusions (0.1%) in 113 patients. The difference in the AR rate in children was significant ($p < 0.0262$). There were no transfusions that caused multiple reactions, and there were no repeat reactions in the pediatric population. There was no significant difference in reaction rates between PAS C and PP when the full data set was parsed by sex (data not shown).

Severity of transfusion reactions

Of the 165 reactions, 158 were considered to be nonsevere (see Table 6). The seven reactions categorized as severe were four ATRs (three PP/one PAS C), two hypotensive transfusion reactions (one PP/one PAS C), and one TAD, caused by a PP transfusion. No transfusion reactions were life-threatening or resulted in death.

DISCUSSION

We report the results of a multicenter study of ARs to PLTs stored in 100% plasma versus PLTs stored in InterSol as part of an open-label, nonrandomized retrospective review. Although other PAS PLTs have been widely used outside the United States, PAS C was the first alternative to PPs available in the United States.

Reactions to PLT transfusions were reported by the clinical staff, but active surveillance was also used to ensure that reactions were not missed. The active surveillance likely accounts for the difference between the historic rate of 0.56% used to calculate the sample size needed for the study versus the overall AR rate of 1.13% reported.[17,18] Reactions were uniformly classified across study sites using NHSN criteria, and an independent, blinded CEC of transfusion medicine experts reviewed all reactions. These measures helped to create a consistent and robust data set.

In an analysis of transfusions that led to ARs, the noninferiority and superiority of PAS C versus PPs were statistically substantiated. It is notable that the data also demonstrated the noninferiority and superiority of PAS C for the two most commonly encountered reactions, ATRs and FNHTRs. Allergens in the plasma have been implicated as the underlying cause for ATRs; therefore, it is logical that a reduction in plasma reduces their rates.[19]

The reduction in FNHTRs may also be related to the reduction in plasma volume. Stored PLTs and WBCs release cytokines and biologic response modifiers into the unit bag over time. These molecules have been implicated as the major mechanism underlying FNHTRs.[7,20,21] Although most of these pyrogenic molecules accumulate over time, some may also be secreted into the plasma at the time of collection.[22] While the time-dependent accumulation of cytokines would not be affected by the replacement of plasma with PAS, the cytokines that are secreted during collection should be partially removed. This reduction in cytokine load may be sufficient to reduce the number of FNHTRs. It may also be that PAS C retards the secretion of cytokines into the unit, although studies with other PAS formulations make this scenario less likely.[23,24] Finally, FNHTRs can be caused by interactions between donor WBCs and recipient antibodies, although it is possible that the converse also occurs. Although the PLTs used in this study were collected from male donors or females tested negative for HLA antibodies, antibodies against WBC antigens may still be present. If there are reactions caused by donor antibodies interacting with recipient WBCs, then a reduction in plasma should cause a concomitant reduction in febrile reactions. The significant reduction in FHNTRs seen in this study may be caused by a combination of these mechanisms. Further studies will be needed to fully understand the role of PAS C in reducing FNHTRs.

Other ARs caused by plasma constituents include acute and delayed hemolytic reactions, TRALI, and hypotensive transfusion reactions. Of these, only hypotensive reactions were reported in this study, but in numbers too

small to comment on significance. All PAS C and PPs were collected using TRALI mitigation strategies, which might account for TRALI's notable absence, although the study was not powered to detect TRALI reactions. Reaction rates for PAS C were significantly less than for PP on both a per-transfusion and a per-patient basis, and repeat allergic reactions were only seen with PP transfusions.

Overall the data showed that patients receiving PP transfusions were more than 3.7 (3.13% vs. 0.83%) times more likely to have a reaction compared to patients receiving PAS C PLT transfusions. It has been shown that a minority of PLT recipients account for the majority of ATRs.[6] While it is possible that PP transfusions caused more repeat ATRs due to patient factors, the overall reduction in ATRs for PAS C points to the plasma content as the most important factor. Data were not collected on whether patients were given pretransfusion medication to prevent reactions. Further, randomized controlled trials have found that pretransfusion medication is not effective in preventing allergic and febrile transfusion reactions in patients who have not had prior reactions.[25,26] A pediatric subgroup analysis found a significant ($p < 0.0262$) difference in ARs for PAS C compared to PP transfusions; however, this study was not powered for this analysis. Nonetheless, the ninefold reduction in reaction rates for PAS C compared to PP is suggestive that PAS C also reduces transfusion reactions in children.

There may be other benefits that result from reduced plasma in the PLT product. The number of PAS C units found to have a high titer of isohemagglutinins has been reported as being significantly reduced for PAS C versus PP units.[27,28] Lower isohemagglutinin levels could potentially make more group O PLTs available for transfusions to patients with other ABO blood groups.

Although transfusion reaction reporting and active surveillance occurred in "real time," this was a retrospective study, which carries inherent weaknesses. Patients were randomly transfused with PP or PAS C, but were not maintained in randomized groups. In addition, pretransfusion medication, which may have been used to reduce allergic and febrile responses, was not tracked. Further, if urticarial reactions were not documented in the electronic medical record, they may have been missed.

ARs cause increased morbidity, and occasional mortality, in transfusion recipients. Reducing the frequency of these reactions can improve patient safety and has been estimated to reduce transfusion reaction management cost between $9 and $11 for each ATR.[29] Additional cost savings from reduced FNHTRs and other ARs may also be realized.

The results of this open-label, multicenter, nonrandomized retrospective study demonstrate the statistical noninferiority, and superiority, of PAS C PLTs compared to PPs in terms of the frequency of mild transfusion reactions. The benefits of PLTs with AS have been demonstrated during the many years that earlier generations of PAS have been used outside of the United States.[14,16,30] The data presented here show that PAS C is a superior product to PP in terms of reduced risk of reactions for patients receiving PLT transfusions.

CONFLICT OF INTEREST

CSC and WAH have received research support/honoraria from Fenwal (a Fresenius-Kabi Company); BB is employed by Fenwal. The remaining authors report no conflict of interest.

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