

The impact of platelet additive solution apheresis platelets on allergic transfusion reactions and corrected count increment

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BACKGROUND: Allergic transfusion reaction (ATR) incidence ranges from 1% to 3% of all transfusions. We evaluated the impact of InterSol platelet additive solution (PAS) apheresis platelets (APs) on the incidence of ATRs and the posttransfusion platelet (PLT) increment.

STUDY DESIGN AND METHODS: This retrospective study evaluated all ATRs among patients at a university hospital that maintained a mixed inventory of PAS APs and non-PAS APs (standard plasma-suspended PLTs). Corrected count increments (CCIs) were calculated for AP transfusions of individuals who received both a PAS and a non-PAS AP transfusion within a 7-day period. Hypothesis testing was performed with chi-square test for dichotomous variables and t tests for continuous variables.

RESULTS: The incidence of ATRs among the non-PAS APs was 1.85% (72 ATRs/3884 transfusions) and 1.01% (12 ATRs/1194 transfusions) for PAS APs (risk ratio [RR], 0.54; 95% confidence interval [CI] = 0.30-0.99; $p = 0.04$). However, there was no difference in the incidence of febrile nonhemolytic transfusion reactions between non-PAS APs (incidence, 0.70%; 27/3884) compared to PAS APs (incidence, 0.59%; 7/1194; $p = 0.69$). Among 223 individuals with paired non-PAS and PAS AP transfusions, the mean CCI at 1 to 4 hours after transfusion was 4932 (95% CI, 4452-5412) for non-PAS APs and was lower for PAS APs (CCI, 3766; 95% CI, 3375-4158; $p \leq 0.001$). However, there was no significant difference in mean CCI at 12 to 24 hours between non-PAS (CCI, 2135; 95% CI, 1696-2573) and PAS APs (CCI, 1745; 95% CI, 1272-2217; $p = 0.14$).

CONCLUSIONS: PAS APs substantially reduce the number of ATRs. CCIs for PAS APs were lower immediately after transfusion, but not significantly different at 12 to 24 hours.

Allergic transfusion reactions (ATRs) are common, with estimates of ATRs ranging from 1% to 3% of all transfusions.¹⁻³ ATRs span from mild urticarial reactions presenting with or without pruritis to severe anaphylactic reactions presenting with dyspnea, hypotension, tachycardia, shock, and in rare cases, death.³

ATRs are difficult to predict and prevent. Both observational and clinical trials have demonstrated that pretransfusion medications administered to prevent ATRs are generally ineffective.⁴ In addition to recipient factors such as atopic predisposition or deficiencies of haptoglobin or immunoglobulin (Ig)A,⁵⁻⁹ rates of ATRs appear to depend on the dose of plasma in the platelet (PLT) product;⁸ concentrating and washing apheresis PLTs (APs) substantially reduce the number of ATRs.¹⁰ However, AP manipulation is time-consuming for medical technologists and increases labor costs; concentrating and washing APs also reduce the number of PLTs transfused and the overall corrected count increment (CCI).¹¹ APs stored in PLT additive solution (PAS) have been shown to reduce

ABBREVIATIONS: AP(s) = apheresis platelet(s);

ATR(s) = allergic transfusion reaction(s); FNHTR(s) = febrile nonhemolytic transfusion reaction(s); PAS = platelet additive solution; RR(s) = risk ratio(s).

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AART was supported by the NIH 1K23AI093152-01A1 and Doris Duke Charitable Foundation Clinician Scientist Development Award (#22006.02).

Received for publication June 19, 2013; revision received October 3, 2013, and accepted October 9, 2013.

doi: 10.1111/trf.12498

TRANSFUSION **,*,**.*.

ATRs,¹²⁻¹⁵ but PAS APs have not previously been available in the United States. The FDA recently approved the use of APs stored in PAS comprising a mixture of 35% plasma and 65% InterSol (Fenwal, Inc., Lake Zurich, IL). If PAS APs significantly reduce ATRs without a significant impact on the CCI, they will likely be cost-effective.¹⁶ This study evaluated the impact of PAS APs on the incidence of ATRs and the posttransfusion PLT increment.

MATERIALS AND METHODS

This retrospective study evaluated the impact of PAS APs on the incidence of ATRs and posttransfusion increment at a large university hospital between June 1, 2012, and December 4, 2012. The study was approved by the Johns Hopkins Medical Institutions Institutional Review Board.

During the study period, a mixed inventory of PAS APs (InterSol, Fenwal) and non-PAS APs (standard plasma-suspended PLTs) was maintained. Recipients of entire AP units, either PAS or non-PAS APs, were included in the study. The majority of the patients requiring PLT support have oncologic diagnoses. PLT transfusion coordinators¹⁷ assigned patients to receive PAS or non-PAS APs without regard to either previous transfusions or transfusion reactions. However, HLA-matched PLTs, comprising less than 10% of our AP inventory, were not collected in PAS. As previously described, patients who had a history of multiple ATRs or severe ATRs received concentrated or washed APs;¹⁰ these individuals did not receive PAS APs.

APs

APs were collected from our community blood center or collected on site by standard procedures.³ PAS APs were collected utilizing the Amicus blood cell separator (Fenwal) and stored in InterSol PAS (PAS-3; Fenwal). The PAS APs were stored in 65% InterSol and 35% plasma. PAS-3 contains citrate, phosphate, and acetate. All APs transfused were irradiated and leukoreduced. One equivalent unit of PLTs was defined as 5.5×10^{10} PLTs, and the AP units contained at least 3.0×10^{11} PLTs.

Concentrated AP units were prepared by reducing the plasma volume of APs by a goal of more than 67% while ensuring that there was at least 100 mL of plasma remaining for resuspension. Washed AP units were prepared by washing the APs with 1 L of normal saline. All washing was performed on a cell processor (Cobe 2991, CaridianBCT, Lakewood, CO).

ATRs

The diagnosis of ATRs was documented at the time of the reaction by transfusion medicine physicians in consultation with the clinical teams. The transfusion medicine

physicians were blinded to the type of AP product transfused. ATRs were clinically diagnosed by the definitions provided in the AABB Technical Manual and the National Healthcare Safety Network Biovigilance definitions.^{3,18} The manifestations of ATRs “form a continuum, with the vast majority clustered at the mild end, in the form of urticaria or ‘hives’—erythematous, sharply circumscribed raised lesions, most often present over the upper trunk and neck, which may itch and which are not usually accompanied by fever or other adverse findings. At the other end of the spectrum are anaphylactic reactions, in which there are systemic symptoms including hypotension, loss of consciousness, shock, and in rare cases death.”³ All diagnosed ATRs were within 6 hours of the transfusion and other potential etiologies of an allergic reaction (e.g., medication, food) were excluded. At Johns Hopkins Hospital, it is an institutional requirement to report all suspected transfusion reactions. PLT transfusion coordinators attend clinical rounds to assist in PLT transfusions and ensure reporting of all transfusion reactions.¹⁷

Many patients may have received pretransfusion medications (diphenhydramine, ranitidine, corticosteroids, acetaminophen, etc.) at the request of their primary physicians. Although there is no institutional policy to recommend or discourage this practice, patients often receive antihistamine pretransfusion medications (diphenhydramine and/or ranitidine) after they have had documented ATRs with prior transfusions. The data on whether pretransfusion medications were administered were not available for rigorous recall, and thus we were not able to include pretransfusion medication history in our analysis.

Assessment of CCI

To ensure equal comparisons of CCI, only those individuals who received both a PAS and a non-PAS AP transfusion within a 7-day period were evaluated. In addition, on the days the two transfusion increments were compared, the patient must have had similar bleeding status (same WHO grade bleeding score), similar maximum temperature (either febrile or not), and posttransfusion labs obtained at 1 to 4 and/or 12 to 24 hours.

CCI values were calculated utilizing the equation

$$CCI = \frac{(\text{PLT count post} - \text{PLT count pre}) \times \text{body surface area (m}^2\text{)}}{\text{number of equivalent units of PLTs transfused}}.$$

The number of equivalent units transfused was calculated by dividing the number of PLTs transfused by 5.5×10^{10} and rounded to the nearest whole number.

The CCI values with the following formula are approximately 1.8-fold lower than CCIs calculated with the alternative formula below.

$$\text{CCI} = \frac{(\text{PLT count post} - \text{PLT count pre}) \times 10^{11} \text{ body surface area (m}^2\text{)}}{\text{number of PLT units transfused}}.$$

Examples of the two calculations are below.

$$\text{CCI (5000)} = \frac{(\text{PLT count post } [25 \times 10^9/\text{L}] - \text{PLT count pre } [10 \times 10^9/\text{L}]) \times \text{body surface area (2m}^2\text{)}}{\text{Number of equivalent units of PLTs transfused (6)}}.$$

$$\text{CCI (9090)} = \frac{(\text{PLT count post } [25 \times 10^9/\text{L}] - \text{PLT count pre } [10 \times 10^9/\text{L}]) \times 10^{11} \times \text{body surface area (2m}^2\text{)}}{\text{Number of units of PLTs transfused (3.3} \times 10^{11}\text{)}}.$$

Statistical analysis

Statistical analyses were performed with computer software (STATA 12, StataCorp., College Station, TX; SAS v9.3, SAS Institute, Cary, NC; and Excel, Microsoft Corp., Redmond, WA). When calculating mean CCI, negative CCIs were imputed to zero. Hypothesis testing was performed with two-tailed t tests (CCI) assuming unequal variance for continuous variables and chi-square tests for dichotomous variables (ATR incidence). Risk ratios (RRs) and 95% confidence intervals (CIs) were estimated using the SAS relrisk frequency procedure. For incidence calculations, the numerator was the number of ATRs and the denominator was the total number of AP transfusions.

RESULTS

ATRs

Between June 1, 2012, and December 4, 2012, there were 604 individuals at a large university hospital who received 3884 unmanipulated non-PAS APs. Of these transfusions, there were 72 ATRs with an incidence of 1.85% (Table 1). Among these 604 individuals who received unmani-

pulated non-PAS APs, there were 345 individuals who received 1194 PAS APs; there were 12 ATRs for an incidence of 1.01%. Thus, PAS APs were associated with a 46% (95% CI, 1%-70%) reduction in ATRs ($p = 0.04$).

During the study period, individuals who previously had clinically significant or multiple urticarial ATRs receive concentrated or washed non-PAS APs at this large university hospital. Thus, individuals who receive manipulated products are a higher risk population for ATRs than the overall patient population who received unmanipulated non-PAS APs or PAS APs. However, compared to PAS APs, the ATR incidence was nonsignificantly lower for concentrated non-PAS APs (incidence, 0.64%; 5/779; RR, 0.64; 95% CI, 0.23-1.81) and washed non-PAS APs (incidence, 0.46%; 2/434; RR, 0.46; 95% CI, 0.10-2.04).

Febrile nonhemolytic transfusion reactions

Table 2 shows the incidence of febrile nonhemolytic transfusion reactions (FNHTRs) for transfused non-PAS and PAS APs. In contrast to ATRs, there was no difference in the incidence of FNHTRs between non-PAS APs (incidence, 0.70%; 27/3884) compared to PAS APs (incidence, 0.59%; 7/1194; $p = 0.69$).

Other transfusion reactions

Of the 3884 unmanipulated non-PAS AP transfusions, there were three (0.08%) reactions of transfusion-associated circulatory overload (TACO), two (0.05%) reactions of transfusion-associated hypotension, and one (0.03%) transfusion-related acute lung injury (TRALI). The community blood supplier confirmed that the symptoms were consistent with TRALI and on further testing found that the male donor had no TRALI risk factors, but identified both anti-human neutrophil antibodies with no definite specificity and four Class II anti-human leukocyte antibodies (HLA). Of the 1194 PAS AP transfusions, there were no TACO, TRALI, or hypotensive reactions. There were no ABO-incompatible hemolytic transfusion reactions for either the non-PAS or PAS AP transfusions during the study period.

TABLE 1. ATR incidence by type of AP transfused

APs transfused	ATRs	Transfusions	Incidence	RR (95% CI)	p value
Non-PAS	72	3884	1.85%	Referent	Referent
PAS	12	1194	1.01%	0.54 (0.30-0.99)	0.04

TABLE 2. FNHTR incidence by type of APs transfused

APs transfused	FNHTR	Transfusions	Incidence	RR (95% CI)	p value
Non-PAS	27	3884	0.70%	Referent	Referent
PAS	7	1194	0.59%	0.84 (0.37-1.93)	0.69

Posttransfusion PLT increment

Among 223 individuals with paired non-PAS and PAS AP transfusions, the mean CCI at 1 to 4 hours after transfusion was 4932 (95% CI, 4452-5412) for non-PAS APs and was lower for PAS APs (CCI, 3766; 95% CI, 3375-4158; $p \leq 0.001$; Table 3). At 1 to 4 hours, there were 132 (59.7%) individuals who received non-PAS APs and 155 (70.1%) individuals who received PAS APs with a CCI below 5000 PLTs $\times$ m² body surface area/ μ L,

TABLE 3. CCI by type of AP transfused

CCI	Non-PAS APs	PAS APs	p value
	Mean (95% CI)		
1-4 hr	4932 (4452-5412)	3766 (3375-4158)	<0.001
12-24 hr	2135 (1696-2573)	1745 (1272-2217)	0.14

which was significantly different ($p = 0.02$). However, there was no significant difference in mean CCI at 12 to 24 hours between non-PAS (CCI, 2135; 95% CI, 1696-2573) and PAS APs (CCI, 1745; 95% CI, 1272-2217; $p = 0.14$). At 12 to 24 hours, there were 70 (65.4%) individuals who received non-PAS APs and 72 (67.3%) individuals who received PAS APs with a CCI below 2500 PLTs $\times$ m² body surface area/ μ L, which was not significantly different ($p = 0.77$).

DISCUSSION

ATRs to APs are the most common problem faced by many transfusion services. Despite pretransfusion medication, many patients continue to experience minor urticarial reactions or severe reactions with allergic pulmonary symptomatology.⁴ This study demonstrates that PAS APs substantially reduce ATRs (46% reduction) without a significant impact on PLT increment at 12 to 24 hours posttransfusion. The findings that PAS decreases ATR incidence to APs by approximately 50% is consistent with previous studies in Europe and Japan.^{12,14,19} Thus, it should now be accepted that PAS APs provide another tool to reduce the incidence of ATRs.

While the data on PAS APs and ATRs are clear, the impact on posttransfusion increments is not as well defined. The initial studies of PLT survival and recovery were variable, but showed that PAS PLT recovery and survival were worse,²⁰ no different,^{21,22} or slightly improved.^{23,24} However, recovery and survival differed based on the type of PAS.^{20,25} The CCI provides better evidence for the impact of PAS APs in vivo. These studies are also mixed; most studies showed no difference²⁶ but some demonstrated that PAS APs were associated with lower CCIs.^{12,14,27} Thus, the findings in this study that the CCIs for PAS APs were lower immediately after transfusion, but not a significant difference at 12 to 24 hours, are consistent with the literature.

We have previously demonstrated that PLT recovery of concentrated and washed AP ranged between 79% and 80%.¹¹ After factoring in the approximately 20% loss of these manipulations, the CCIs of concentrated APs at 1 to 24 hours were similar to non-PAS APs.¹¹ However, the CCIs of washed APs were 19% to 41% lower at 1 to 24 hours posttransfusion compared to non-PAS APs.¹¹ Since PAS

APs were 24% lower at 1 hour and 18% lower at 24 hours compared to non-PAS APs in this study, PAS APs are likely equivalent to concentrated APs and superior to washed APs in terms of CCI.

Although the pathophysiology of ATRs has not been fully elucidated, both donor plasma and recipient components play a role in ATRs.⁶ While recipient characteristics are involved (e.g.,

IgA-, haptoglobin-, C3-, or C4-deficient individuals who form existing IgG or IgE antibodies),^{7,28-32} there is also clearly a donor component. Previous studies have demonstrated that ATR incidence is dependent on the dose of plasma in the PLT product.^{8,10} Biogenic amines, eosinophil and neutrophil chemotactic factors, enzymes, leukotrienes, prostaglandin, PLT-activating factor, and numerous cytokines have all been found in the plasma and implicated in ATRs.^{8,28,33} It has also been demonstrated that the transfusion of allergens (e.g., penicillin, aspirin, ethylene oxide, and even some food allergens) have been associated with ATRs.³⁴⁻³⁷ This study confirms that the plasma component of APs has an essential role in the etiology of ATRs. Further understanding of the pathophysiology of ATRs could provide the basis of new preventative techniques.

We have previously demonstrated that concentrating APs reduces ATRs by 73% and washing APs reduces ATRs by 95%.¹⁰ This study suggests that concentrating and washing APs are likely more effective in reducing ATRs than PAS APs. Limitations of concentrating and washing APs is that these manipulations utilize considerable blood bank resources and time and reduce the CCI by 20% to 40%.¹¹ However, concentrating and washing APs should still be considered for highly sensitized individuals while further research is conducted on additional means to reduce ATRs. In addition, concentrating PAS APs may be more advantageous to reduce ATRs than concentrating non-PAS APs if an ISBT code for this product and manipulation becomes available.

In addition to morbidity and mortality from potential adverse clinical effects, ATRs lead to increased health care expenditure by prolonging the time required by physicians, nursing staff, and technologists for the transfusion procedure and the evaluation of ATRs, as well as by requiring additional resources to address the ATRs directly. Mild ATRs typically require treatment with antihistamines, and severe ATRs can lead to costly hospitalization for outpatients or prolonged hospital stays for inpatients. Using PAS APs is cost-saving for hospital transfusion services when the additional cost of PAS charged to the transfusion providers is less than \$9.14.¹⁶ If pretransfusion medication could also be eliminated, PAS APs would be cost-saving while the additional cost of PAS storage is less than \$11.90.¹⁶ Thus, APs stored in PAS may be a financially and clinically appealing strategy to prevent ATRs.

PAS APs may have benefits in addition to reducing ATRs.¹³ Since TRALI is due to either bioactive substances or antibodies to HLA or neutrophil antigens in the donor plasma, reduction of donor plasma exposure by 65% in PAS AP products may have a beneficial impact in decreasing this transfusion reaction. However, since very small quantities of residual plasma are capable of causing TRALI,³⁸ further research is needed. The rates of bacterial contamination in PAS APs compared to non-PAS APs have not been fully investigated. However, PAS appears to facilitate bacterial detection and may be useful in pathogen inactivation technologies.¹⁵ In addition, transfusion of ABO-incompatible plasma APs is associated with hemolytic transfusion reactions with a risk that ranges from 1 in 2000 to 1 in more than 46,000 transfusions.³⁹⁻⁴³ The AABB Standards state that “the transfusion service shall have a policy concerning transfusion of components containing significant amounts of incompatible ABO antibodies or unexpected red cell antibodies.”⁴⁴ The reduced volume of plasma in PAS APs will likely reduce risk of ABO-mismatched hemolysis. The reduction of plasma used in APs will also permit additional plasma to be available for fractionation. However, due to the reduced plasma content, PAS APs may not be as appropriate for patients with low levels of clotting factors, such as massive transfusion patients.

Due to the retrospective nature of this study, there are limitations to this study. We were unable to determine the infusion rate for the transfused products or whether patients received pretransfusion medications before the transfusion. Antihistamine pretransfusion medications are often used at our institution by the clinical teams after one ATR. In the past 10 years, three of four studies concluded that prophylactic medication with diphenhydramine does not reduce the incidence of ATRs.⁴⁵⁻⁴⁷ In addition, two randomized, double-blind, placebo-controlled trials demonstrated that 25 mg of diphenhydramine does not reduce the overall risk of ATRs.^{48,49} Thus, there is very little evidence that the current regimen of diphenhydramine has any influence on ATRs.⁴ Consequently, pretransfusion medication likely does not have any effect on the results of this study. The ineffectiveness of pretransfusion medications to prevent ATRs gives greater credence to use effective methods such as plasma reduction to reduce ATRs.

We hope that the results from this study may assist in reducing ATRs. Assuming that the incremental costs are commensurate with the benefits, an acceptable strategy may include the following: 1) patients without a coagulopathy receive PAS APs since these products contain 65% less plasma; 2) patients who are sensitive to ATRs (i.e., they have had previous minor ATRs) receive PAS APs; and 3) patients who continue to have ATRs be given concentrated or washed APs. As always, chronic PLT

recipients should be carefully monitored with PLT counts to maintain adequate PLT levels.

ACKNOWLEDGMENT

We appreciate the laboratory medical technologists who performed the transfusion reaction work-ups.

CONFLICT OF INTEREST

Johns Hopkins University has previously received research support from Fenwal, Inc. Except for RJB who is a consultant for Fenwal, all authors declare no conflict of interest.

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