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Transfusion and component characteristics are not associated with allergic transfusion reactions to apheresis platelets

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Abstract

Background—Transfusion-related characteristics have been hypothesized to cause allergic transfusion reactions (ATRs) but they have not been thoroughly studied. The primary objective of this study is to evaluate the associations of infusion rate, infusion volume, ABO mismatching, component age, and premedication with the incidence and severity of ATRs. A secondary objective is to compare the risk of these attributes relative to the previously reported risk factor for aeroallergen sensitization in transfusion recipients, as measured by an aeroallergen-specific IgE antibody screen.

Study Design and Methods—Clinical and transfusion-related data were collected on subjects with reported ATRs and uneventful (control) apheresis platelet transfusions over a combined 21 month period at two academic medical centers. Control transfusions were selected as the next uneventful transfusion after an ATR was reported. Logistic regression, Mann-Whitney and t tests were used to assess associations with ATRs. Previously reported aeroallergen-specific IgE screening data was incorporated into a multivariable logistic regression.

Results—143 ATRs and 61 control transfusions were evaluated among 168 subjects, ages 2-86 years. Infusion rate, infusion volume, ABO mismatching, component age, and premedication showed no statistically significant association with ATRs ($P>0.05$). Neither infusion rate nor infusion volume increased the risk of anaphylaxis vs. mucocutaneous only ATRs. Aeroallergen sensitization has previously been associated with ATRs. After controlling for transfusion-related covariates, aeroallergen sensitization remained statistically significantly associated with ATRs (OR 2.68, 95%CI: 1.26-5.69).

Conclusions—Transfusion and component-specific attributes are not associated with ATRs. An allergic predisposition in transfusion recipients is associated most strongly with ATR risk.

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Keywords

allergic; transfusion reaction; apheresis platelet

INTRODUCTION

Allergic transfusion reactions (ATRs) are a common complication of blood transfusion, particularly platelet transfusion. Overall, the incidence of ATRs to platelet transfusions is 1-4%[1,2]. The plasma fraction of platelet components appears to harbor the allergic stimulus for ATRs[1,3,4]. In unusual circumstances, recipient antibodies[5-7] or passive transfusion of donor antibodies[8-12] can cause ATRs. However, these risk factors do not explain most ATRs. A pervasive risk factor appears to be individuals with an allergic predisposition[13], specifically aeroallergen sensitization[14-17].

Component and transfusion-related factors may also influence the risk of ATRs, but they have not been thoroughly studied. Premedication[18], transfusion rate, ABO compatibility[19], component age[20], and platelet source[21] have been hypothesized to affect the risk of ATRs. These are modifiable risk factors, so understanding their role in ATRs is important for designing transfusion strategies that minimize the impact of ATRs.

MATERIALS AND METHODS

Study design

The study design, population, and methods have been described previously[16]. Briefly, patients with ATRs reported to the blood bank at Johns Hopkins Hospital (JHH) from July 2011 to May 2012 and Brigham and Women's Hospital/Dana Farber Cancer Institute (BWH/DFCI) from November 2012 to August 2013 were invited to enroll. Previously enrolled subjects who experienced subsequent ATRs during the study period were included as additional ATR cases. The study was IRB approved at both institutions and informed consent was obtained from all subjects. Control transfusions were selected as the patient receiving the next platelet component issued to a non-surgical location after an ATR was observed. The enrollment ratio of ATR:control subjects was targeted at 2:1. The study was designed to have 80% power to detect a 20% absolute difference in atopic disease prevalence between ATR subjects and controls. Medical histories were obtained by a research coordinator via structured patient (and family, as appropriate) questionnaires and chart reviews. Allergic histories and ATR manifestations have been reported previously[16]. Infusion rate, total volume transfused, ABO typing, platelet age, and premedication data were collected at the time of enrollment. Reaction severity was coded as mucocutaneous (i.e. skin and/or mucosal symptoms only) or anaphylaxis (i.e. mucocutaneous plus respiratory, cardiovascular, or gastrointestinal symptoms), according to consensus criteria[22] and review by an allergist. All platelet components were collected by apheresis. Plasma aeroallergen-specific IgE multiallergen screen analysis (Phadiatop, ThermoFisher Scientific/Phadia, Kalamazoo, MI) has been reported previously[16]. A clinically positive test was defined as ≥ 0.35kUa/L.

Statistics

Summary statistics are presented as mean ± SD or median (interquartile range, IQR) for continuous variables and as proportions for binary variables. Data were log transformed for statistical testing when transformation achieved normality, as assessed by the Shapiro-Wilk test. Unpaired, two-tailed t tests with unequal variance were used to compare continuous variables between groups for normally distributed values. Mann-Whitney U tests were used to compare continuous values for non-normally distributed variables. Comparisons of proportions between groups were performed with a two-tailed Fisher's exact test. For logistic regression, a complete case analysis was used (n=158 observations: 45 controls (74%) included; 113 ATR cases (79%) included) with robust variance estimation. Statistical significance was defined as $P<0.05$ and a confidence interval that does not include 1, for odds ratio (OR) estimates. Analysis was conducted with Stata v13.1 (StataCorp, College Station, TX).

RESULTS

Platelet transfusions

During the study period, 143 ATRs and 61 control transfusions were evaluated among 168 subjects, ages 2-86 years. Criteria for anaphylaxis were met in 26 ATRs (18.2%). Among all subjects, 59% were male (n=99). Six platelet components were concentrated, four of which caused ATRs. Two components were washed, both of which caused ATRs. In 41 transfusions (28 ATRs and 13 control), two platelet components were transfused consecutively as a continuous infusion. In these instances, the second component was a split from the same donation in 24 transfusions. Of subjects with at least 1 ATR and 2 platelet transfusions before enrollment, 33% (34/103) had at least one additional ATR.

Transfusion rate and volume

The mean infusion rate of apheresis platelets was 6.3 ± 3.5 mL/min. Mean weight-normalized infusion rates were 0.094 ± 0.074 mL/kg/min. Mean infusion rates were 40% higher at BWH/DFCI than JHH (0.11 vs. 0.081 mL/kg/min, respectively; $P=0.005$). Figure 1A shows the infusion rates (mL/kg/min) in apheresis platelet transfusions that did or did not result in an ATR. Mean infusion rates were 8% slower in the ATR group than in the control group (0.092 vs 0.10 mL/kg/min, respectively; $P=0.5$). To evaluate whether infusion rate is related to severity of ATRs, we compared ATR infusion rates in mucocutaneous only reactions to anaphylaxis (Figure 1B). Mean infusion rates were 29% higher in anaphylactic vs. mucocutaneous only reactions, but the difference was not statistically significant (0.087 vs. 0.11 mL/kg/min, $P=0.3$).

In addition to infusion rate, total infusion volume could plausibly be a risk factor for ATRs if the allergic stimulus is dose dependent. Subjects who received two consecutive platelet products represent a group who receive twice as much component volume as the rest of the cohort. However, a similar proportion of controls received double transfusions (13 of 61, 21.3%) as those who experienced ATRs (28 of 143, 19.6%, $P=0.8$). We also evaluated the total transfusion volume on a mL/kg basis for all subjects. The total volume transfused was similar between ATR and control groups (mean 4.5 vs. 4.2 mL/kg, respectively; $P=0.2$). The

volume transfused was not statistically different between mucocutaneous only vs. anaphylactic ATRs (*P*=0.8).

ABO mismatched transfusion

ABO mismatch transfusion was assessed as major (cellular incompatibility), minor (plasma incompatibility), or any mismatch. Of all transfusions, 48% were ABO mismatched. Table 1 shows the proportion of ATR and control transfusions that were mismatched. There were no statistically significant differences between ATR and control groups (Table 1).

Storage duration

The median age of platelets in the study was 5 days. Platelet storage age was not statistically different between transfusions that did or did not result in an ATR (*P*=1). There was no difference in the proportion of younger platelets between the ATR and control groups. Platelet components causing ATRs were 2 or 3 days old in 14.3% of units, compared to 9.8% of control units (P=0.5).

Premedication

We assessed the frequency of diphenhydramine, H2 receptor antagonist, and glucocorticoid premedication prior to transfusion (Table 2). In some cases, patients received these drugs for underlying medical conditions, and medication administration coincidentally preceded transfusion. Thus, diphenhydramine dosing within six hours prior to transfusion and H2 receptor antagonist or glucocorticoid dosing within 24 hours prior to transfusion was considered a premedication. There were no statistically significant differences in premedication frequency, although patients with ATRs tended to receive diphenhydramine premedication more often. Two percent of subjects (4 of 204) received an H1 receptor antagonist other than diphenhydramine in the 24 hours preceding transfusion (2 control: loratadine, hydroxyzine; 2 ATR: both loratadine).

Logistic model of ATR risk

In univariable logistic regression, the following covariates were analyzed: infusion rate (mL/min), any ABO mismatch, component age, diphenhydramine premedication, and glucocorticoid premedication. None of these variables was statistically significantly associated with ATRs (*P*>0.05 for all analyses, Table 3). Similar results were seen in multivariable analysis. Addition of an interaction term to measure the effect of combined diphenhydramine and glucocorticoid premedication was not statistically significant in multivariable analysis, which included all covariates (*P*=0.6).

A previous report from this cohort identified that concentrations of aeroallergen-specific IgE (Phadiatop) are directly related to the frequency of ATRs[16]. Phadiatop screen results were available on 86% of subjects. Of subjects with at least one ATR to apheresis platelets, 55.9% (62/111) had a positive Phadiatop screen. Of subjects without an ATR, 28.6% (10/35) had a positive Phadiatop screen. Among subjects with recurrent ATRs (n=34), 28 had Phadiatop screen results. The Phadiatop screen was positive in 78.6% (22/28) of subjects with recurrent ATRs. In univariable analysis of the current study, a positive aeroallergen-specific IgE screen was associated with the risk of an ATR (Table 3, *P*=0.007). Having a

positive aeroallergen-specific IgE screen remained statistically significantly associated with ATRs when controlling for all of the component and transfusion-related variables (Table 3, P=0.01).

DISCUSSION

The goal of this study is to determine the extent to which variability in component and transfusion-specific attributes are associated with ATRs. We do not find evidence of an association of any component or transfusion-specific factor with ATRs.

It would seem biologically plausible that slowing the rate of infusion of an offending agent would reduce the adverse reaction rate. This is commonly observed in medication administration[23] and drug desensitization protocols[24] but was not observed in this study. Similarly, antihistamines mitigate symptoms of type I hypersensitivity reactions[25], so it would seem plausible that they could prevent ATRs. Unfortunately, several RCTs and cohort studies have indicated that antihistamine premedication does not prevent ATRs[18,26-29]. Thus, available evidence does not support routinely slowing infusion rates or providing antihistamine premedication for the prevention of ATRs. It has not been established whether certain subsets of patients, e.g. those with an atopic predisposition, may benefit from premedication or whether combination therapy with different anti-allergy medications can prevent ATRs.

Aeroallergen sensitization is a risk factor for ATRs. Aeroallergen-specific antibodies may be directly involved in the mechanism of ATRs, e.g. cross reactivity with human proteins, or these antibodies may be a surrogate for another type of allergic predisposition. Azuma and colleagues demonstrated that sera from people who experienced ATRs caused more spontaneous histamine release from mast cells than controls, as measured by calcium influx[13]. Thus, mast cells may be more primed to react in sensitized subjects.

There are limitations to our study. As all platelet components in the study were apheresis derived, a comparison between single donor and pooled, whole blood derived platelets was not possible. However, data from an RCT with prospective evaluation for transfusion reactions showed no difference in allergic transfusion reaction rates between pooled and single donor platelet components[1]. As this study was observational, we did not control component selection, premedication, or infusion rates. Infusion rates may have varied systematically across providers and care units with different ATR reporting patterns, thereby introducing bias into our results. In addition, many patients who are likely more prone to allergic transfusion reactions were the ones who likely received pre-medications. We did not collect data on providers or care units, so it remains possible that imbalances in infusion rates are due to selection bias from particular care areas. Nevertheless, the vast majority of ATRs occurred among patients with hematologic malignancy and those undergoing hematopoietic stem cell transplantation who are cared for in a select few care units, where nursing practices tend to be consistent. Generalizability of these observations is increased because data were collected from two separate hospital systems. Controlled clinical trials would be necessary to address the causality of each of the transfusion-specific factors addressed in this study.

In summary, we do not find evidence that variability in platelet component and transfusion-specific characteristics are associated with ATRs. Mechanistic studies on the nature of transfusion recipient allergic sensitization and the necessary plasma factors that combine to generate ATRs are required to understand how to best prevent these reactions from occurring.

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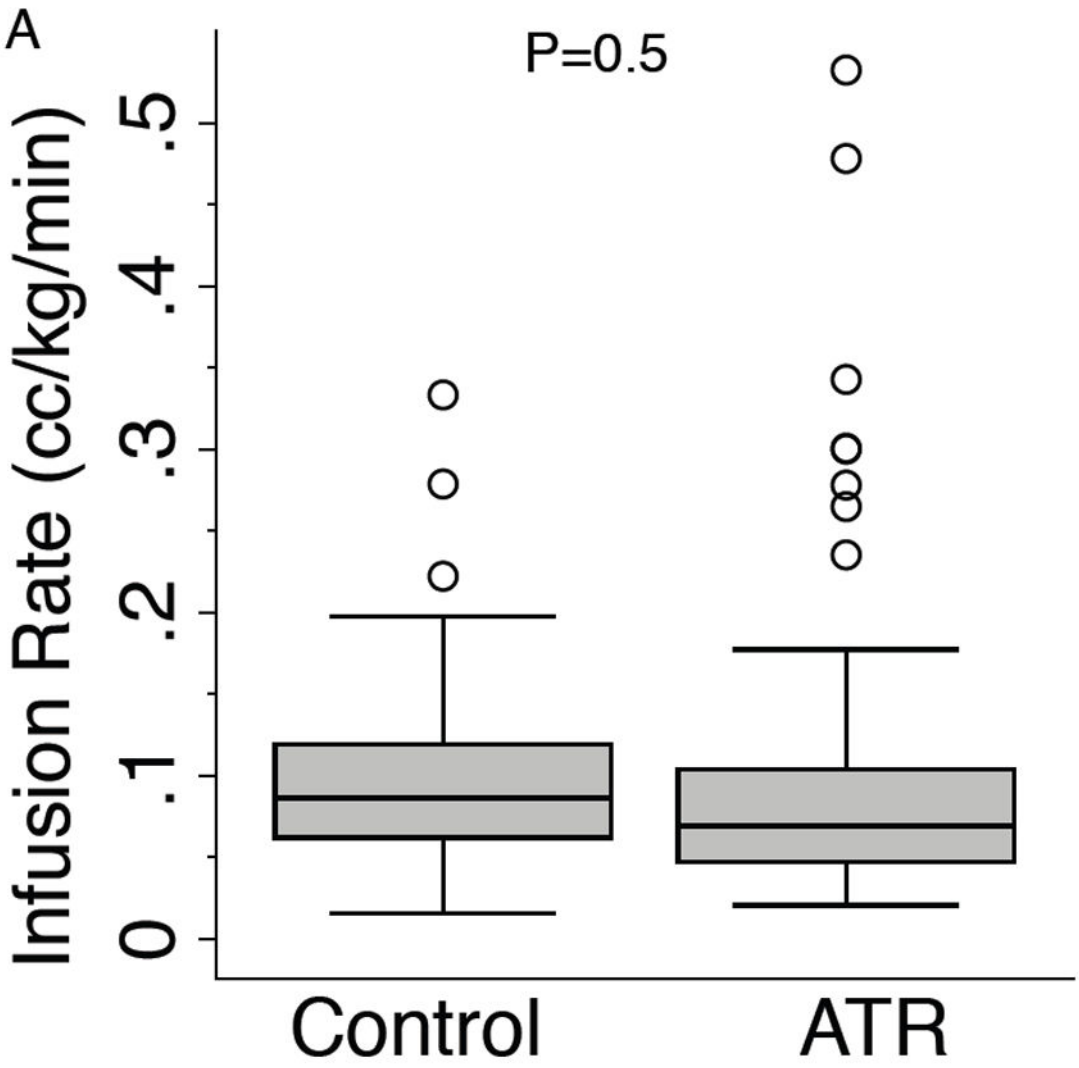

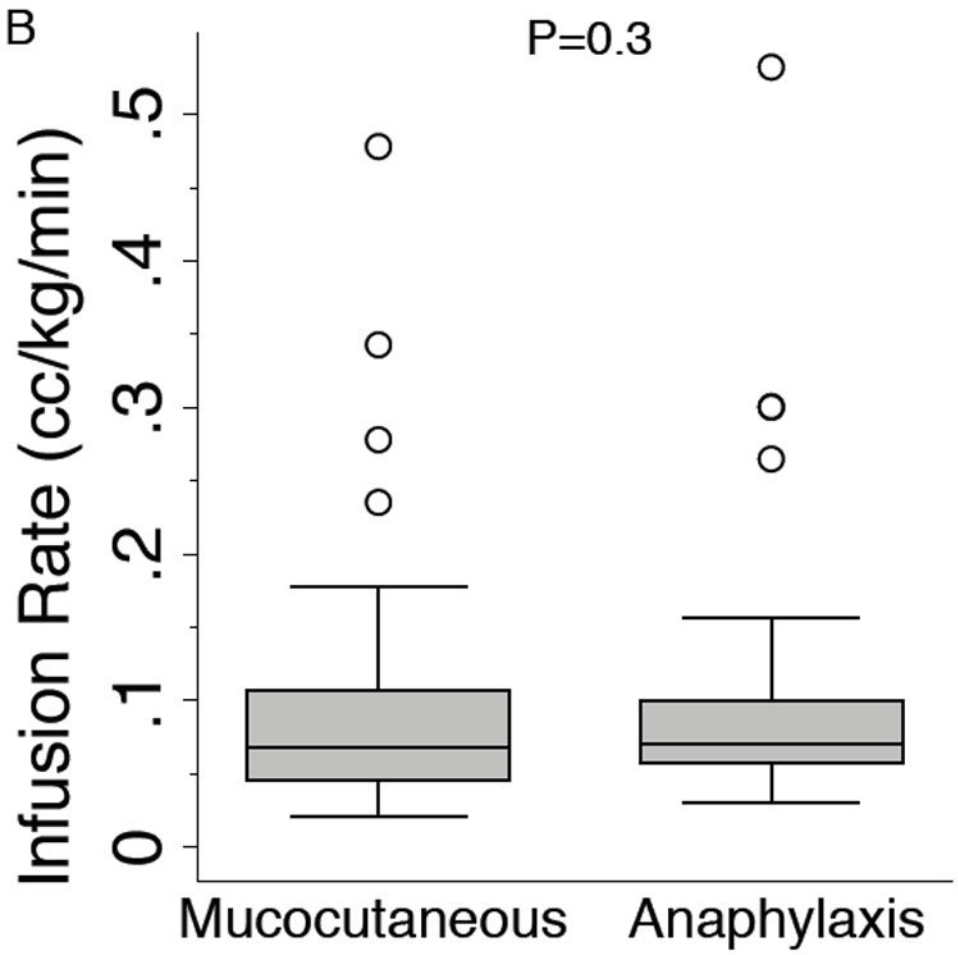

Figure 1. Infusion rates of apheresis platelets and their association with incidence and severity of ATRs

A. Infusion rates (mL/kg/min) in uneventful transfusions (n=51) and ATRs (n=124). B. Infusion rates in ATRs that were mucocutaneous only (n=98) vs. ATRs that involved two or more systems (anaphylaxis, n=26).

Table 1

ABO mismatch in ATR and control transfusions

ABO Mismatch	No ATR (n=61)	ATR (n=143)	*P*
Minor	11 (18%)	17 (11.9%)	0.3
Major	25 (41%)	56 (39.2%)	0.9
Any	32 (52.5%)	66 (46.2%)	0.4

Table 2

Documented pre-transfusion medication*

Medication	Control	ATR	*P*
Diphenhydramine	17 (27.9%)	60 (42.3%)	0.06
H2 receptor antagonist†	10 (16.4%)	33 (23.4%)	0.3
Glucocorticoids†	11 (18%)	16 (11.3%)	0.3

* <1%missing data

† In the 24h prior to transfusion

Table 3

Logistic regression estimates of ATR risk (n=158)

	Univariable		Multivariable	
Covariate	**OR**	**95% CI**	**OR**	**95% CI**
Infusion rate (cc/min)	0.91	0.81-1.01	0.9	0.81-1.01
Component age (days)	0.89	0.58-1.35	0.74	0.47-1.18
Any ABO mismatch	0.69	0.35-1.39	0.69	0.33-1.44
Diphenhydramine premedication	1.28	0.62-2.64	1.23	0.54-2.78
Glucocorticoid premedication	0.45	0.16-1.23	0.42	0.15-1.2
Positive aeroallergen-specific IgE screen	2.68	1.31-5.49	2.67	1.26-5.69