

Transfusion reactions: a comparative observational study of blood components produced before and after implementation of semiautomated production from whole blood

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BACKGROUND: A semiautomated method of component production from whole blood was implemented at Canadian Blood Services. To assess safety of the new components, the frequency of adverse transfusion events (ATEs) to platelet components (PCs) and red blood cell (RBCs) produced before and after implementation of the new method was surveyed and compared.

STUDY DESIGN AND METHODS: This retrospective, observational, noninferiority study was conducted in 12 sentinel hospitals across Canada. The control group received RBCs in additive solution-3 (AS-3) and platelet-rich plasma (PRP)-produced platelets (PLTs) for 3 to 11 months before implementation of semiautomated production, and the study group received RBCs in saline-adenine-glucose-mannitol (SAGM) and buffy coat (BC)-produced PLTs for 3 to 11 months after implementation. ATE definitions at each hospital and standard practice for reporting did not change between control and study periods. Data for analysis were obtained from databases and original report forms.

RESULTS: The pooled risk ratio of a reaction to SAGM versus AS-3 RBCs was 0.77 (95% confidence interval [CI], 0.66-0.90), suggesting that SAGM products had significantly lower reaction rates than AS-3 products ($p < 0.01$). Reported allergic reactions to RBCs decreased from 0.07% (AS-3) to 0.04% (SAGM). For PLTs, the difference in reaction rates between BC and PRP was not significant ($p = 0.37$), and the pooled risk ratio of BC versus PRP was 1.14 (95% CI, 0.86-1.50).

CONCLUSION: The change in manufacturing method was associated with lower reaction rates to SAGM RBCs than to AS-3 RBCs. Pooled BC PLTs were noninferior to random-donor PRP PLTs with respect to ATEs.

Although increasingly safe, transfusion of any type of blood component can potentially lead to an adverse transfusion event (ATE). Beyond ATEs arising from infections with bacterial, viral, and other agents, noninfectious complications of blood transfusion and the occurrence of laboratory and nursing errors in patient identification currently represent the greatest risk to patients.¹ Types of ATEs vary, from febrile nonhemolytic transfusion reactions (FNHTRs), which are most common and often mild,² to allergic reactions and potentially fatal reactions, for example, transfusion-related acute lung injury (TRALI). Due to differences in ATE definitions and reporting, as well as different reaction incidence and type depending on the blood component being transfused, rates of ATEs are difficult to determine absolutely. However, ATEs are more frequent after transfusion of platelet components (PCs) than of red blood cells (RBCs) or plasma.²

In recent years, several risk-minimization strategies have been successful in reducing adverse event rates in all blood components. For example, the preferential use of

ABBREVIATIONS: AS-3 = additive solution 3; ATE(s) = adverse transfusion event(s); BC = buffy coat; CBS = Canadian Blood Services; FNHTR = febrile nonhemolytic transfusion reaction; PC(s) = platelet component(s); PRP = platelet-rich plasma; SAGM = saline-adenine-glucose-mannitol.

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TRANSFUSION **,***.**.

male plasma³ and prestorage leukoreduction⁴ have helped to reduce ATEs, which were previously cited to occur in as high as 2% to 31% of PC transfusions.⁵⁻⁸ ATE rates differ depending on many factors including storage time and the method of preparation of the component, with higher rates often seen in PCs prepared by the platelet-rich plasma (PRP) method versus buffy coat (BC) or apheresis-derived PCs.^{9,10}

Between 2005 and 2008, Canadian Blood Services (CBS) implemented a change in its method of component production from whole blood, phasing out manual production and introducing semiautomated production processes.¹¹⁻¹³ This change had an impact on all blood components produced by CBS. Before, platelets (PLTs) were produced from whole blood using the PRP method,^{14,15} with leukoreduction of components taking place after separation. This process resulted in random-donor PCs which had to be pooled to generate an adult transfusion dose, as well as plasma components and leukoreduced RBCs in additive solution-3 (AS-3) preservative. PLT production is not applied to all whole blood donations at CBS, and when PLTs were not required a hard spin was used to separate RBCs and plasma from filtered whole blood, also resulting in plasma components and leukoreduced AS-3 RBCs. After the introduction of semiautomated production, PLTs were produced using the BC method, in which four BCs are pooled during production, and the PLTs separated and leukoreduced to generate a pooled PLT concentrate that equates to one adult transfusion dose.¹¹ RBCs are leukoreduced and stored in saline-adenine-glucose-mannitol (SAGM) preservative. Similar to before introduction of the new processing method, when PLTs are not required an alternative whole blood filtration method is used which produces plasma components and leukoreduced SAGM RBCs.¹²

The new process was introduced because of its significant benefits, including increased process control during production, increased recovery of plasma for fractionation, and a greater yield of PLTs, which can be provided as pooled, recipient-ready components to hospitals. However, these benefits must not compromise recipient safety. As part of the requirements for regulatory approval of this new (to Canada) manufacturing method, the effect of this change in component production on adverse events to PLT and RBC components was assessed, with monitoring of ATEs at 12 major hospital centers across Canada in the months before and after the change. The aim of this monitoring study was to determine if there was a change in the rate of ATEs in patients receiving transfusion before compared with after the implementation of the new production method. The hypothesis tested was that blood components produced after implementation of semiautomated processing would not be inferior, that is, would not cause higher rates of ATEs, compared with blood components produced before implementation.

MATERIALS AND METHODS

Study design

The study was designed as a pre- and postimplementation observational study, with the control group receiving transfusions before the implementation of semiautomated production and the study group receiving transfusions after the implementation of semiautomated production. The study was conducted at 12 major hospital centers across Canada. The monitoring period was 3 months ($n = 10$ sites) or 11 months ($n = 1$ site) before and after implementation or 11 months before and 9 months after implementation ($n = 1$ site). The unit of observation was the blood component being transfused. Ethical approval was not necessary as this was an observational study of a routine practice using licensed blood products. Furthermore, regulatory authorities did not deem that this data collection activity constituted a clinical trial. All patients received blood components according to local practice and the decision to transfuse was taken by the treating physician and not influenced by the study. Hospitals were aware that CBS was changing component manufacturing platforms; hospital customers were informed of the change through a series of customer letters in 2005¹⁶ and a circular of information for BC components. Training to spike the new blood component bags was undertaken before implementation of the new products and the most visible change was the introduction of a prestorage pooled PLT product. The extent to which this knowledge may have biased the study outcome was not assessed. Pretransfusion medication was not recorded as part of the study. The patient's identity was not available to the analyst at any time.

Component production

Manual component production (control group)

Semiautomated production was implemented at CBS between 2005 and 2008.¹¹⁻¹³ Before this, manual production was used. All whole blood donations were collected in citrate-phosphate-double dextrose. When PLT production was required (approx. 48% of whole blood donations), the PRP or soft spin-hard spin production method was used. Briefly, whole blood was processed within 8 hours into PLTs, plasma, and RBCs using a closed system that produces leukoreduced whole blood-derived PLT products (Leukotrap RC-PL system, Pall Canada Ltd, Mississauga, ON).¹⁷ Testing of PLT units for bacterial contamination using the Hong Kong sampling method¹⁷ was in effect at some CBS sites; therefore, 23% of PRP PLT units were tested for contamination and 77% were not. Single-donor PCs were produced, and depending on local practice, four to six of these were pooled at the hospital laboratory or at the bedside to make one adult therapeutic dose. The RBCs were leukoreduced using filtration and suspended in AS-3

preservative. When PLTs were not required (approx. 52% of whole blood donations), the whole blood was filtered to remove white blood cells, a hard spin was used to separate RBCs from plasma, and the RBCs were suspended in AS-3 preservative. Throughout the study, PLTs produced before implementation of semiautomated production were referred to as PRP PCs (based on the PLT production process) and RBCs were referred to as AS-3 RBCs (based on the preservative).

Semiautomated production (study group)

All whole blood donations were collected in citrate-phosphate-dextrose. When PLT production was applied to the donation (approx. 55% of whole blood donations), the BC method was used.^{11,17} Briefly, whole blood was rapidly cooled to 18 to 24°C and held overnight before processing. Units were collected into top-and-bottom collection sets (MacoPharma, Mouvaux, France). Components were separated into RBCs, BC, and plasma using a hard spin and RBCs and plasma were simultaneously extracted using a semiautomated extracting device (Compomat G4, Fresenius-Kabi, Bad Homburg, Germany). RBCs were suspended in SAGM. PCs were produced by pooling four BCs in 1 unit of plasma, subjecting the pool to a soft spin to separate the PLTs, and then passing the PLT concentrate through a leukoreduction filter. All PLT pools were subjected to bacterial culture using a bacterial detection system (BacT/ALERT, bioMérieux Canada, Inc., St Laurent, Quebec, Canada) with an 8-mL aerobic culture at least 24 hours after whole blood donation. The pools were delivered as one transfusion dose to the hospital laboratory. Whole blood not intended for BC-PLT production (approx. 45% of whole blood donations) was collected using top-and-top collection sets, with bags manufactured by either MacoPharma or Fenwal, Inc. (Lake Zurich, IL), depending on the collection site. After an overnight hold, the whole blood was leukoreduced by filtration, before centrifugation to sediment RBCs and semiautomated extraction of components (Compomat G4). The resultant RBCs were suspended in SAGM. Throughout the study, PLTs produced after implementation of semiautomated production were referred to as BC PCs (based on the production method) and RBCs were referred to as SAGM RBCs (based on the preservative).

Data analysis

Data collection

Data on all transfusion reactions were captured using existing procedures and protocols. Compiled data on ATEs, the same information that was provided to the hemovigilance network, were sent by the hospital blood banks to the investigators. The number of units transfused for each product code was obtained from hospital databases. There was some hospital-to-hospital variation in

pooling practice for PRP PLTs, with 10 of the sites pooling 5 units to make a transfusion dose, one site pooling 4 units to make a transfusion dose, and one site pooling 6 units to make a transfusion dose. The definitions for ATEs already in place at each center were used. Most centers used the Transfusion Transmitted Injury Surveillance System (TTISS) guidelines¹⁸ and thus definitions were mostly harmonized between sites with only slight differences found. These included minor differences in the types of reaction reported by hospitals (e.g., some reported citrate-mediated toxicity and others did not) as well as some differences in definitions and symptoms of reactions. However, definitions used at each site did not change between the control group and the study group. The primary endpoint of the study was the frequency of ATEs and the secondary endpoint was the frequency of reaction types in periods before and after implementation of semiautomated production.

Statistical analysis

Reaction rates before and after implementation of the new production method were calculated for each study site. The risk ratio and its 95% confidence interval (CI) were used to describe the difference in reaction rate. The ratio was calculated by dividing the rate of reactions after implementation by the rate before implementation. A ratio of less than one suggested that the postimplementation reaction rate was lower than the preimplementation reaction rate, and for the 95% CI, either a lower bound greater than 1 or an upper bound less than 1 suggested that the difference was significant ($p < 0.05$).

Since the study sites (hospitals) had their own transfusion and ATE reporting practice, the difference in reaction rates may not be affected by implementation of the new production process only, but also by hospital transfusion practice (cluster). Therefore, a meta-analysis was conducted to find pooled effects for all 12 hospitals. Data, including total number of transfusions and number of transfusion reactions for RBCs and PLTs, were entered into computer software (Review Manager, Version 5.0, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2008, <http://ims.cochrane.org/home>). A heterogeneity test was conducted first to determine whether the studies were homogenous. If the test yielded a p value of less than 0.05, a random-effects model was used to find the pooled effect (reaction risk ratio); otherwise, a fixed-effects model was used. The pooled effect was calculated as a weighted average of risk ratios from all the study sites with inverse variance being site weight.

RESULTS

RBC ATEs

The total number of AS-3 RBCs transfused during the study period before the implementation of semiauto-

mated production was 110,218 units. After implementation, 88,765 SAGM RBC units and 23,367 AS-3 RBC units were transfused. Reactions to AS-3 RBC units transfused after implementation of the new method were excluded from the analysis.

Reported ATE rates (as a percentage of transfused units/site) to AS-3 RBCs ranged from 0.09% to 0.96%, with a median of 0.38%, and for SAGM RBCs, rates ranged from 0.10% to 0.57%, with a median of 0.29% (Table 1). Ten of 12 hospitals reported lower or similar reaction rates for SAGM compared with AS-3 RBCs, with three of these (Sites 4, 6, and 9) reaching significance based on the upper bounds of the 95% CI for the risk ratio ($p < 0.05$). Two hospitals reported increased reactions to SAGM RBCs (from 0.09% to 0.32% and from 0.39% to 0.54% at Sites 8 and 12, respectively).

The pooled risk ratio of reactions to RBCs comparing SAGM with AS-3 was 0.77 with a 95% CI of 0.66 to 0.90, suggesting that transfusion of SAGM RBC components resulted in significantly lower reaction rates (23%, $p = 0.001$). Since the heterogeneity test showed marginal significance ($p = 0.07$), a random-effects model was also fitted to find the pooled risk ratio, which was 0.75 (95% CI, 0.59-0.96).

For 10 of the sites, all data provided regarding types of ATEs were analyzed (Fig. 1). Reactions classified as "unknown" or "undetermined" by the hospitals were excluded from the analysis. Based on total transfusion numbers of 105,059 and 86,263 for AS-3 and SAGM RBCs, respectively, the most common reactions were FNHTRs (0.16% of transfused units for both groups), followed by minor allergic reactions (0.07 and 0.04% for AS-3 and SAGM RBCs, respectively).

PLT ATEs

The number of PRP doses transfused during the study period before the implementation of the semiautomated BC method was 11,416 and the number of BC PCs transfused after implementation was 9908. There were 1188 PRP PLT transfusion doses given after the implementation of the BC method and reactions to these were excluded from the analysis.

For PRP PC transfusions, the reported ATE rates ranged from 0.00% to 4.48%, with a median of 0.96%, and for BC PCs the reaction rates ranged from 0.00% to 20.00%, with a median of 0.97%. These ranges included several extreme values: no reactions were reported at Site 7 (for BC PC) and Site 8 (for PRP PC), and a reaction rate of 20% was reported at Site 11 for BC PCs, based on a low sample size of three reactions after 15 transfusions (Table 2). Seven hospitals had lower or similar reaction rates for BC PCs while five had higher rates (Site 1, 1.57% vs. 1.15%; Site 5, 0.33% vs. 0.20%; Site 8, 3.45% vs. no reactions; Site 9, 1.14% vs. 0.58%; and Site 11, 20.00% vs.

1.30% for reaction rates to BC PCs and PRP PLTs, respectively).

A heterogeneity test was not significant ($p = 0.16$), so a fixed model was used to find pooled effects for the meta-analysis. Contrary to the RBCs, the difference in reaction rates between BC PCs and PRP PLTs was not significant ($p = 0.37$), and the pooled risk ratio of BC PC versus PRP was 1.14 (95% CI, 0.86-1.50). Based on the upper limit of 95% CI (1.50), BC PCs were not inferior to PRP PLTs in terms of ATE rate. This conclusion also held when noninferiority was defined as less than 2.0 times higher reaction rates after BC PC transfusion than after PRP PLT transfusion.

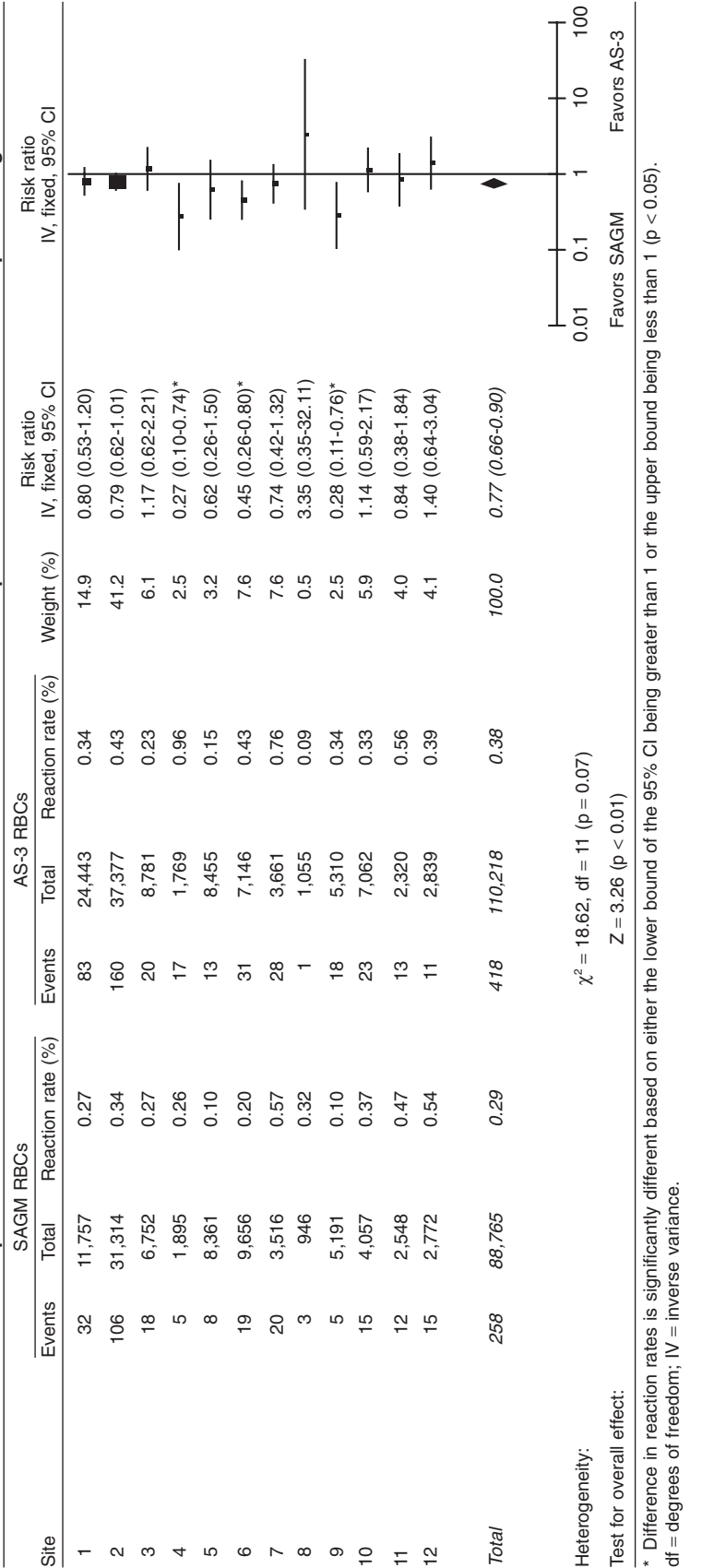
For 10 of the hospital sites, data on the types of reactions occurring after PLT transfusions were analyzed (Fig. 2). Based on total transfusion numbers for PRP and BC PCs of 10,897 and 9556, respectively, the most frequent type of reaction to PCs was minor allergic reactions (0.30 and 0.38% for PRP and BC PCs, respectively), followed by FNHTRs (0.24 and 0.17% for PRP and BC PCs, respectively).

DISCUSSION

The introduction of semiautomated production processes at CBS represented a widespread change in manufacturing that affected all components. Although it is still unclear whether production methods affect clinical performance,¹⁹ for PLTs there is much in vitro evidence to suggest that BC-produced components display superior storage characteristics to those produced by the PRP method.²⁰ This, together with advantages the semiautomated process offered in terms of increased plasma recovery and the logistics of manufacturing process,¹⁵ led to the implementation of this change.

Introduction of the new process resulted in changes to the final products: for example, the anticoagulant contains less glucose, whole blood is held overnight before processing rather than being processed within 8 hours, and RBCs are stored in SAGM rather than AS-3. For PCs, the change in production meant pooling of PLTs takes place during production at CBS rather than at hospitals. The impact of such considerable changes was assessed at the level of the component using in vitro assays,¹¹⁻¹³ but ultimately the impact at the level of the recipients of the products needs to be determined. To this end, this study demonstrated that in terms of ATEs, the new production process generated components that either were associated with significantly fewer reactions (RBCs) or were at least not worse (PLTs) than manually produced components. The lower ATE rate observed with SAGM RBCs could be related to the different storage solution used. Another difference that could likely influence adverse events is the lower volume of residual plasma in these units. For SAGM RBCs produced using the BC method, mean plasma content ranges from 10 to 29 mL (based on

TABLE 1. Forest plot and reaction rates after RBC transfusions before and after implementation of semiautomated processing



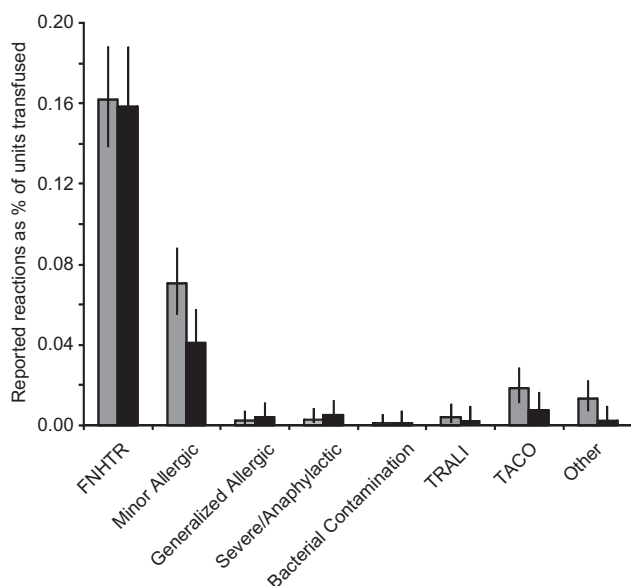


Fig. 1. Types of ATEs after transfusion of RBCs. The incidences of different types of transfusion reactions (as % of total transfusions) to AS-3 RBCs (□) and SAGM RBCs (■), captured from 10 hospital sites, are shown. Vertical lines on the bars represent 95% CIs. The most common type of reaction to RBCs was FNHTR, with an incidence of 0.16% of transfusions for RBCs produced by either method. The category “other” contains adverse events that did not fit into any of the defined categories, but excludes adverse events that were categorized by the reporting hospitals as “unknown” or “undetermined.” It should be noted that no hemolytic transfusion reactions were recorded after RBC transfusions. TACO = transfusion-associated circulatory overload.

calculations using CBS quality control data for hematocrit and unit volumes), while for AS-3 RBCs from a unit from which PRP PLTs have also been prepared, the mean plasma content ranges from 10 to 56 mL.

In this study, rates of ATEs were assessed using compiled data sent to the investigators by the hospital blood banks. The criteria for reporting reactions in this study were similar across all the hospitals, as they were based on the TTISS guidelines.¹⁸ However, criteria were not identical and differences and inconsistencies in reporting can occur in studies such as this.^{2,21} Importantly though, criteria at the individual hospitals did not change during the study and were the same before and after implementation of the new process. Furthermore, although the data used in this study were the same as those provided to the hemovigilance network, we do not know the extent to which some events were not captured or reported, and this represents a potential limitation of the study. It has previously been observed that awareness of reporting transfusion reactions increases every time a novel process or product is introduced. This is most likely a conse-

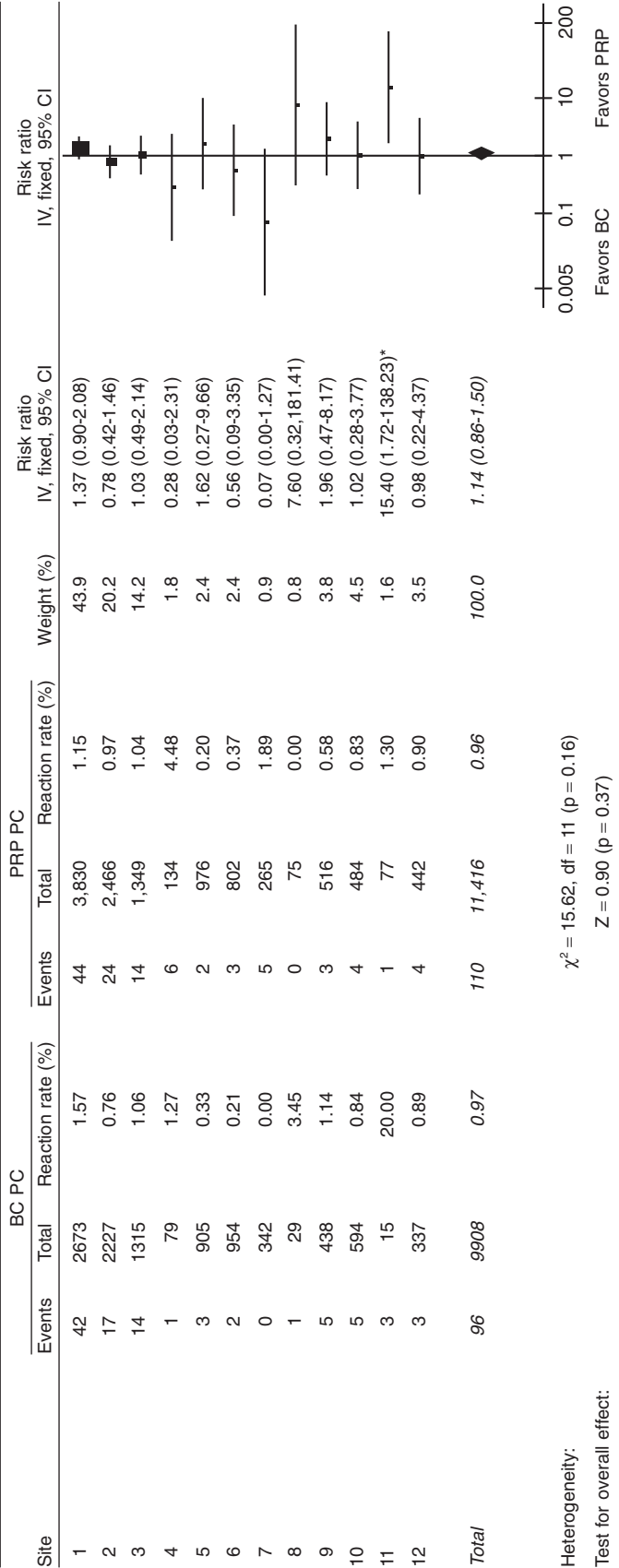
quence of the increased education and training of staff that occurs with the implementation of new measures. As habits are difficult to maintain, the increased number of reports tends to decrease again over time, an effect that could also influence reporting of reactions.

Previously reported reaction rates for leukoreduced RBCs range from 0.2%⁸ to 3% (for allergic transfusion reactions²²), similar to the rates found in this study. Only two hospitals reported increased reactions to SAGM RBCs and these increases can be considered modest (increases of 0.1% in both cases) and well within what have been reported in the literature. The types of reactions reported, and the finding that the most common reactions to RBC were FNHTRs, also correspond to previous reports.⁸ Similarly, the mean reaction rate to PLTs (approx. 1%) is similar to or lower than those in recent reports for allergic transfusion reactions.^{22,23} In our study, the most common type of reaction to PLTs was found to be minor allergic reactions. FNHTRs are often reported as the most common transfusion reaction to PLT products,²⁴ although minor allergic reactions are also common, particularly with PLTs stored in plasma.²³ It is also worth noting that the capture of transfusion reactions, particularly FNHTRs, which are characterized by increase in temperature of at least 1°C, can be influenced by pretransfusion medication with antipyretics,⁸ information that was not available as part of this study.

In general, ATEs are more common with PLTs than with either RBCs or plasma,^{2,6} and previous studies have demonstrated that single-donor apheresis PLTs or BC PLTs result in fewer transfusion reactions than PRP PLTs,^{7,9} although many of these studies are older and refer to products before the implementation of universal leukoreduction. In this study, a significant reduction in ATEs to BC PLTs compared to PRP PLTs was not found; however, BC PLTs were not found to be inferior to PRP PLTs. This was a retrospective monitoring study, and the window examined was 3 months before and after implementation for most sites, resulting in low numbers of transfusions and events for some of the smaller hospitals included in the study. Also, the collection of data was based on reported reactions per component, not reported reactions per recipient. Although there is increasing evidence that transfusion reactions are more associated with donor and recipient factors than with the component,²³ reactions are rare events and this approach was chosen because if the criteria for statistical testing were too stringent, a single patient having repeated reactions could significantly skew the data.

In conclusion, blood components produced using semiautomated production methods do not induce a higher rate of transfusion reactions compared with blood components produced using manual methods. Indeed for RBCs, the rate of reactions is significantly less after implementation of the new production process than previously.

TABLE 2. Forest plot and reaction rates after PLT transfusions before and after the implementation of the BC method



* Difference in reaction rates is significantly different based on either the lower bound of the 95% CI being greater than 1 or the upper bound being less than 1 ($p < 0.05$).
 df = degrees of freedom; IV = inverse variance.

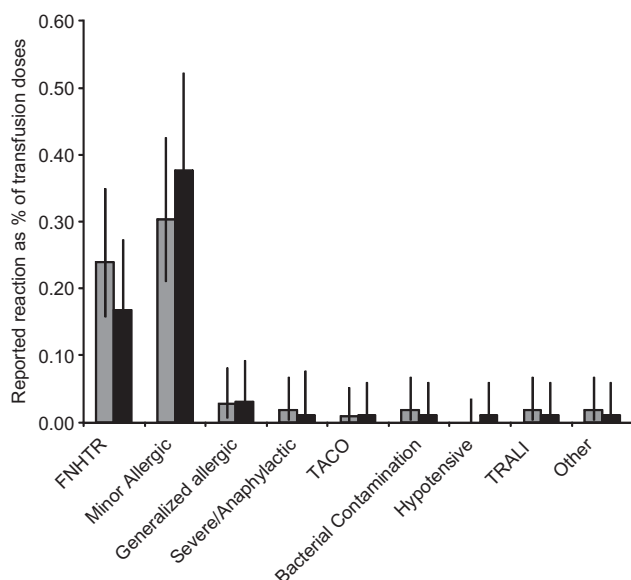


Fig. 2. Types of ATEs after transfusion of PLTs. The incidences of different types of transfusion reactions (as % of total transfusions) to PRP PCs (□) and BC PCs (■), captured from 10 hospital sites, are shown. Vertical lines on the bars represent 95% CIs. The most common type of reaction to either PRP or BC PCs is minor allergic reactions. The category “other” contains adverse events that did not fit into any of the defined categories, but excludes adverse events that were categorized by the reporting hospitals as “unknown” or “undetermined.” TACO = transfusion-associated circulatory overload.

Although the reduction in rates with components produced with semiautomated methods are modest, particularly compared with the large reduction in ATE rates seen with earlier method improvements such as leukoreduction^{4,25} and the predominant use of male plasma to prevent TRALI,^{3,26,27} these improvements are significant and reduce the potential for morbidity in recipients of blood components.

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CONFLICT OF INTEREST

There are no conflicts of interest for the authors of this publication.

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