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Lack of Persistent Microchimerism in Contemporary Transfused Trauma Patients

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Abstract

BACKGROUND: Following transfusion, donor white blood cells (WBCs) can persist long-term in the recipient, a phenomenon termed transfusion-associated microchimerism (TA-MC). Prior studies suggest TA-MC is limited to transfusion following traumatic injury, and is not prevented by leukoreduction.

STUDY DESIGN AND METHODS: We conducted a prospective cohort study at a major trauma center to evaluate TA-MC following injury. Index samples were collected upon arrival, prior to transfusion. Follow-up samples were collected at intervals up to one year, and beyond for those testing positive for TA-MC. TA-MC was detected by real-time quantitative allele-specific polymerase chain reaction assays at the HLA-DR locus and several polymorphic insertion deletion sites screening for non-recipient alleles.

RESULTS: 378 trauma patients were enrolled (324 transfused cases and 54 non-transfused controls). Mean age was 42±18 years, 74% were male, and 80% were injured by blunt mechanism. Mean Injury Severity Score was 20±12. Among transfused patients, median (interquartile range) number of red cell units transfused was 6(3,12), and median time to first transfusion was 9(0.8,45) hours. Only one case of long-term TA-MC was confirmed in our cohort. We detected short-term TA-MC in 6.5% of transfused subjects and 5.6% on non-transfused controls.

CONCLUSIONS: In contrast to earlier studies, persistent TA-MC was not observed in our cohort of trauma subjects. Short-term TA-MC was detected, but at a lower frequency than previously observed, and rates were not significantly different than what was observed in non-transfused controls. The reduction in TA-MC occurrence may be attributable to changes in leukoreduction or other blood processing methods.

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Keywords

Microchimerism; trauma; white blood cells; leukoreduction

INTRODUCTION:

The presence of donor white blood cells (WBCs) in transfused blood products can cause problems in the recipient ranging from alloimmunization, a recipient immune response against donor antigens, to transfusion-associated graft versus host disease (TA-GVHD), in which the donor's WBCs mount an immune response against the recipient. In most cases, residual donor WBCs do not survive for long in transfusion recipients, generally clearing within a couple of weeks after transfusion.[1,2] Following traumatic injury, however, donor-derived WBCs from transfused blood have been found in the circulation long after transfusion, a phenomenon termed microchimerism.[2–7] It is not known if these cells are the result of long-term survival or hematopoietic engraftment, but they appear to represent a diverse array of cell subsets, suggestive of engraftment.[2] Evidence suggests donor-derived cells can persist for months, years, or in some cases, decades after transfusion, and can account for up to 5% of the circulating WBC population.[2–7] Rates of microchimerism vary by study, with conservative estimates in the 10–20% range and some rates as high as 45–50%.[2–9]

To date, efforts to detect transfusion-associated microchimerism (TA-MC) in other patient populations (such as HIV-infected, elective surgery, pediatric, and postpartum hemorrhage patients) have, for the most part, failed to find microchimeric populations, suggesting that this phenomenon may generally be restricted to transfusion following traumatic injury.[2,10–12] Traumatic injury causes profound immune dysregulation, including both immunosuppressive and immune stimulating components, and involving major changes in RNA expression profiles, circulating cytokines, and other immune mediators.[13,14] This altered environment may be a key factor in enabling the establishment of persistent microchimerism. The one example of TA-MC occurring outside of traumatic injury is from a recent study that found evidence of microchimerism in pediatric recipients of whole blood in Ghana.[15] While the study was small and had some limitations, the finding is compelling and merits further study.

Because of the risks associated with donor WBCs, efforts are made to reduce the number of donor WBCs in transfused blood products through leukoreduction. Leukoreduction processes are not standardized, and techniques and products for leukoreduction continue to evolve, but current methods can reduce the number of WBCs from ~5×10^8 WBCs/unit to less than 1×10^6 WBCs/unit. These reductions in transfused WBCs have significantly reduced (though not eliminated) the risks of TA-GVHD and alloimmunization.[16–19] Surprisingly, three studies comparing trauma patients transfused with non-leukoreduced versus leukoreduced blood found no significant difference in rates of microchimerism between these groups, suggesting that the reduced number of WBCs in leukoreduced blood are still sufficient to establish TA-MC.[4,8,9]

Studies of TA-MC to date have utilized relatively small patient cohorts. These smaller sample sizes have made it difficult to identify predictive factors and have detected variable rates of TA-MC. In this study, we sought to evaluate the prevalence, magnitude, and natural history of TA-MC in a larger cohort of transfused trauma patients.

MATERIALS AND METHODS:

Study Enrollment

We conducted a prospective cohort study of injured patients enrolled at the University of California, Davis, Medical Center (UCDMC), a Level I trauma center serving the greater Sacramento region. Prior approval was obtained for this study from the Institutional Review Boards (IRBs) at the University of California (UC), Davis and San Francisco campuses, and BloodSource. Subjects were enrolled between December 2, 2006 and July 31, 2010. We considered as potentially eligible all injured patients who triggered activation of the most urgent level of triage upon arrival to the emergency room. We focused enrollment on patients who had suffered blood loss, who had a blood sample available from a specimen drawn shortly after arrival (prior to any transfusion), and who were likely to receive blood transfusion and survive to hospital discharge. Some of these patients ultimately did not receive any blood transfusion, and we enrolled a subset of these patients as non-transfused controls. We excluded patients under 12 years old, prisoners, and those with a known previous bone marrow or solid organ transplantation. The UC Davis IRB granted us permission to collect the initial blood specimen prior to obtaining consent; we approached each eligible transfused patient and a subset of non-transfused patients (or their surrogates) to obtain informed consent for all subsequent study activity (analysis of the initial blood sample and collection and analysis of subsequent blood samples including chimeric assessment and chart review), in accordance with our approved protocol. See Figure 1 for a flow chart of the study enrollment.

Blood products

Blood products were sourced from BloodSource, now part of Vitalant. The vast majority of red blood cells (RBCs) units used in this study were AS-1 packed RBCs, with a small number of AS-3 and CPDA-1 packed RBCs used as well. No fresh whole blood was used. Platelets, plasma, and cryoprecipitate were used in some patients (see Table 1). A small number of irradiated packed RBCs nearing expiration may have been used to avoid waste.

Sample collection and processing

Blood samples were collected into 10 mL plastic Vacutainer K_2EDTA spray-coated tubes (BD, Franklin Lakes, NJ) at UC Davis. The sample tubes—which were dedicated for use in this study—were not opened or subjected to any testing prior to being shipped overnight via FedEx to Vitalant Research Institute, formerly Blood Systems Research Institute, in San Francisco, arriving within 72 hours of collection. Upon arrival, an aliquot was centrifuged, the majority of the plasma fraction was removed, and the remaining concentrated cellular fraction was mixed by gentle pipetting, frozen, and stored at −80°C. Frozen samples were thawed in batches for DNA isolation in which red cells were lysed and WBC pellets were washed before extracting DNA, as previously described.[8]

We sought to collect index (pre-transfusion) samples upon the patient's arrival in the Emergency Department at UCDMC, and follow-up samples at periodic intervals up to 1 year (7, 14, 28, 90, 180, and 365 days) following injury, and past one year (every six months, up to three years) after injury if long-term microchimerism was observed. We considered subjects to have completed participation if they tested negative for microchimerism at one year or more after injury, and we considered their participation incomplete if samples were not collected up to this point.

Assessment of TA-MC

TA-MC was assessed using a combination of two different real-time quantitative allele specific polymerase chain reaction assays (QAS-PCR) as previously described.[8] Briefly, each of these assays is designed to detect minor populations of non-recipient WBCs at either the HLA-DR locus or at several polymorphic insertion deletion (InDel) sites on nine different chromosomes.[4,20] Using this combination of assays we estimate that there will be an informative allele in 99.5% of donor-recipient pairings, and we have demonstrated high sensitivity, with the ability to detect the presence of a single chimeric cell.[2,20–22] DNA was isolated from washed WBC pellets to exclude cell-free DNA that might be present in the plasma. Index samples were used to genotype subjects and identify informative alleles (i.e. non-recipient alleles not detected at high copy numbers within the index sample), with follow-up samples screened for these specific alleles. Samples were considered microchimeric if four out of four replicates had a cycle count less than or equal to 40 for a non-recipient allele at any of the tested loci. Short-term microchimerism was defined as having at least one positive sample between day 10 and day 179 post-injury. Long-term microchimerism was defined as having at least one positive sample 180 days or more post-injury.

Statistical Analysis.

We limited our analyses to subjects who had at least one follow-up sample collected at least 10 days after the index specimen. We compared baseline characteristics of non-transfused and transfused subjects using the chi-square, t-, and Mann-Whitney U tests. The proportion of transfused cases and non-transfused controls with detected microchimerism were compared using a one-sided Fisher's exact test.

RESULTS:

A total of 377 transfused subjects and 74 non-transfused control subjects were enrolled in the study, for a total of 451 subjects (Figure 1). Of these, 44 did not have at least one follow up sample collected, and 29 additional subjects did not have follow up samples collected at least 10 days post-index, resulting in a total of 378 evaluable subjects, including 324 transfused cases and 54 non-transfused controls. We collected long-term follow-up samples (≥180 days post-injury) on a total of 244 subjects (209 transfused cases and 35 non-transfused controls). A total of 1252 follow-up samples were collected (Figure 2A).

Non-transfused and transfused subjects had similar age, sex, and mechanism of injury (Table 1). Transfused subjects had a greater likelihood of presenting with hypotension and greater

injury severity than non-transfused subjects. Transfused subjects received a median of 6 (IQR 3, 12) units of red blood cells, including 2 (1, 7) during the first 48 hours, and the median time from arrival until first transfusion was 9 (0.8, 45) hours.

Short-term microchimerism (observed between days 10–180) was confirmed in 21 of the transfused cases (6.5%) and 3 of the non-transfused controls (5.6%). An additional short-term microchimeric case was detected among the transfused cases, but excluded as it was only detectable at 102 days post-index, and not at 17, 34, 223, 349, or 459 days post-index, suggesting a transient response to a secondary exposure. A single long-term microchimeric case (lasting beyond 180 days) was confirmed among the transfused cases (0.5%). Long-term microchimerism was detected in an additional 2 transfused cases, however, each of these was ruled out for different reasons. In one case we were able to recall all of the blood donors and none was a match for the detected chimeric cells. While this chimeric population was not seen at index, our index samples were smaller with less DNA input. These samples were screened predominantly for recipient genotype and the assay may not have had enough sensitivity at that DNA input level to detect a small, preexisting chimeric population, which may have also expanded in the dysregulated immune environment following trauma. Signal was seen at 4, 17, 47, and 194 days post-index, resolving by 569 days post-index. In the second suspect case, a chimeric population was seen at 344 days post-index, but not at 14, 112, or 1100 days post-index, suggesting that this may be the result of a secondary exposure. Overall, 22 of the 324 transfused cases (6.8%) and 3 of the 54 non-transfused controls (5.6%) had any confirmed microchimerism, and comparison by Fisher’s exact test showed no significant difference between these rates (p=0.51).

The timing of the samples screened for all subjects as well as the non-transfused controls and those with some confirmed microchimerism are plotted in Figure 2A. The distribution of these samples was similar within the non-transfused controls and the overall population, and within the group with detected microchimerism and the overall population. Among transfused subjects, the median time from the last known red cell transfusion to the last study specimen was 340 (IQR 23, 413) days. The analysis of which samples had a detectable chimeric population among the confirmed microchimeric cases is plotted in Figure 2B. For the 3 microchimeric non-transfused controls, all were positive at only a single time-point within the first 2 months. Of the 22 microchimeric transfused cases, 14 were only detected at a single time-point.

Evaluation of leukoreduction quality control data collected in 2008 (in the middle of our study) from BloodSource, who supplied the blood used at UCDMC, captured a reduction in residual WBCs following a change from whole blood leukoreduction to a spin-first approach in April of that year (Figure 3A). While the loss of microchimerism appears to have occurred prior to the start of the current study in 2006, earlier changes in practice may have produced similar reductions in residual WBCs to account for this loss. Evaluation of more recent quality control data for 2018/2019 shows an even greater reduction in residual WBC counts since the time of our study, presumably through further refinement of leukoreduction practice (Figure 3B).

DISCUSSION:

In this study, we prospectively evaluated 324 transfused and 54 non-transfused trauma patients for TA-MC, including pre-transfusion samples on all subjects shortly after presentation, and a total of 1252 follow-up samples to screen for chimeric populations both in the short-term (10–180 days after transfusion) and long-term (>180 days after transfusion). The observed rates of TA-MC within this study were much lower than expected with only 7% of transfused cases confirmed to have any detectable microchimerism, compared with 6% of non-transfused controls. While rates of TA-MC have been shown to be very low or absent in other types of patient cohorts,[10–12] we have previously found that rates of persistent TA-MC among transfused trauma patients range from ~10–30%, with even higher rates of short-term TA-MC (Table 2).[4,5,23]

This paucity of TA-MC we observed is surprising, given that the current study cohort, while larger than earlier studies, is otherwise similar. In fact, one of our earlier studies, which detected short-term TA-MC rates of 64% and long-term TA-MC rates of 26%, was conducted at the same trauma center only a few years earlier than the current study, and used the same clinical accrual, sample processing, and TA-MC assays.[4] In that cohort of injured patients, as well as another one in which we observed TA-MC,[8] the age, sex, mechanism of injury, Injury Severity Score, and amount and timing of transfusion of patients were similar to the present study.

The detection of short-term TA-MC in our non-transfused controls was also surprising. This may simply represent the baseline false positive detection rate inherent to the highly sensitive PCR assay we used. Consistent with this, all of the 3 non-transfused controls were positive for a microchimeric population at a single time-point. Another possibility is that they received transfusions after enrollment that were not known to us (e.g., occurred at another hospital or were not recorded in the medical record at UCDMC). Alternatively, these controls may have had undetectable pre-existing chimeric populations that temporarily expanded in response to the immunological stress of traumatic injury.[13,14] Subsets of these subjects were included in a study of anti-HLA alloimmunization (55 transfused and 17 non transfused).[18] While none of the non-transfused controls tested positive for new anti-HLA antibodies (compared with 11/55 transfused cases), 4 of the 17 non-transfused controls did have preexisting anti-HLA antibodies (3/55 for transfused cases), suggesting a previous alloexposure in some subjects.

One explanation for the disappearance of TA-MC could be changes in leukoreduction and overall blood processing techniques. While earlier studies in the U.S., and one contemporary study in Australia, did not see differences in the rates of TA-MC between recipients of leukoreduced and non-leukoreduced blood (Table 2),[4,8,9] leukoreduction and blood processing procedures vary widely between blood providers and are continuously evolving. Differences can include blood collection methods, types of filters used, the timing of filtration versus centrifugation, use of different additives, and many other variables. Improvements to leukoreduction practices have led to modest incremental reductions in residual WBCs (Fig. 3), potentially crossing a threshold needed for establishment of microchimerism. These updated leukoreduction practices may also have resulted in changes

in which populations of WBCs are ultimately removed from the transfused product. If a particular subset of cells is required for TA-MC, such as circulating $CD34^+$ stem cells, and a change in processing differentially impacts this subset, it could explain loss of TA-MC, even if the change results in a small difference in the total number of residual WBCs. This idea is difficult to assess directly, as evaluating the phenotype and function of small numbers of residual WBCs in large volumes of blood presents significant technical challenges. If however, this hypothesis is correct, TA-MC may continue to occur in other populations of transfused trauma patients, as blood processing and leukoreduction methods vary considerably.

Acknowledgments

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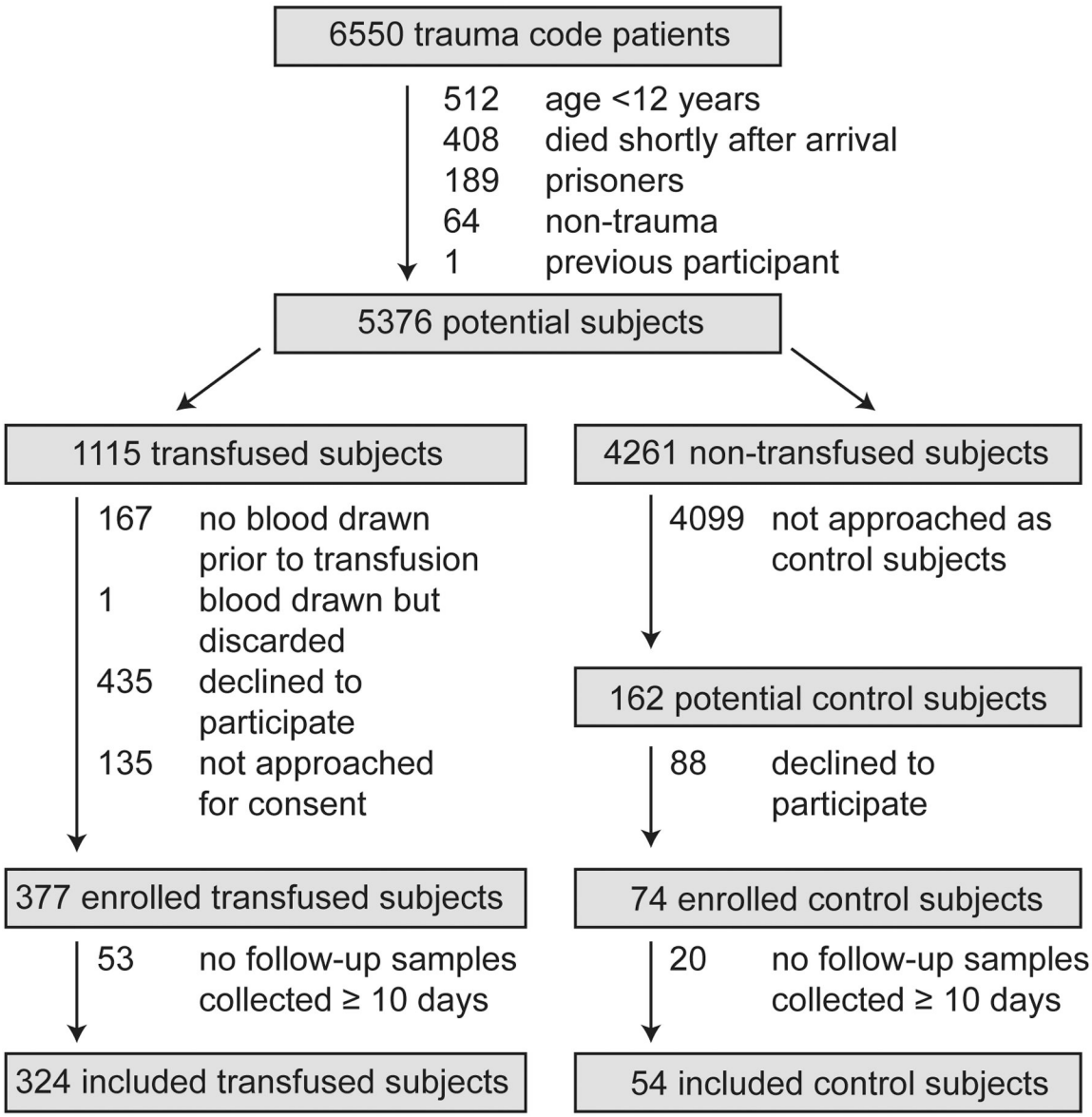

Figure 1.
Study enrollment flow chart.

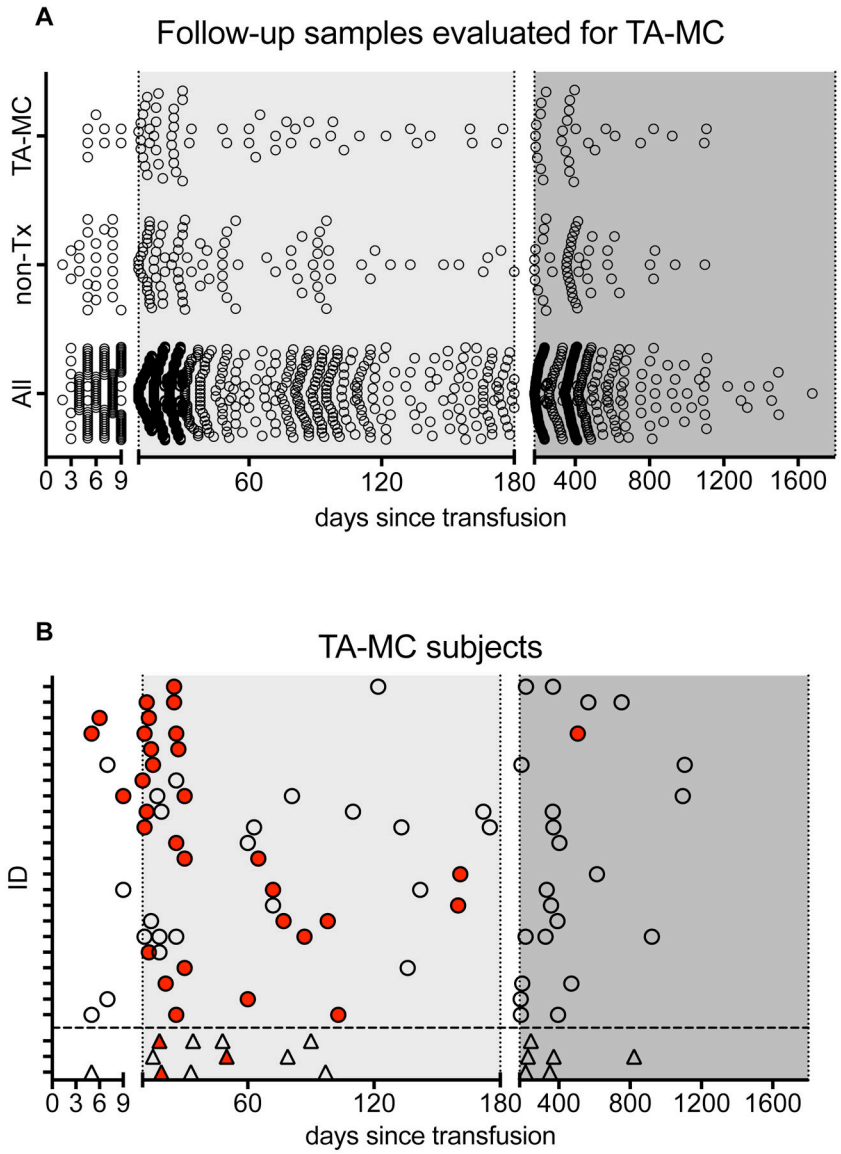

Figure 2. Samples screened for TA-MC.

(A) Plots the samples screened over time for all subjects, as well as the subset of non-transfused controls and those with detected TA-MC. (B) Plots the samples screened over time for subjects with at least one sample positive for TA-MC, positive samples are shown in red. Triangles below the dashed line represent non-transfused controls. Light grey region indicates the time frame considered short-term TA-MC (10–180 days post-index) and dark grey region indicates the time frame considered long-term TA-MC (>180 days post-index).

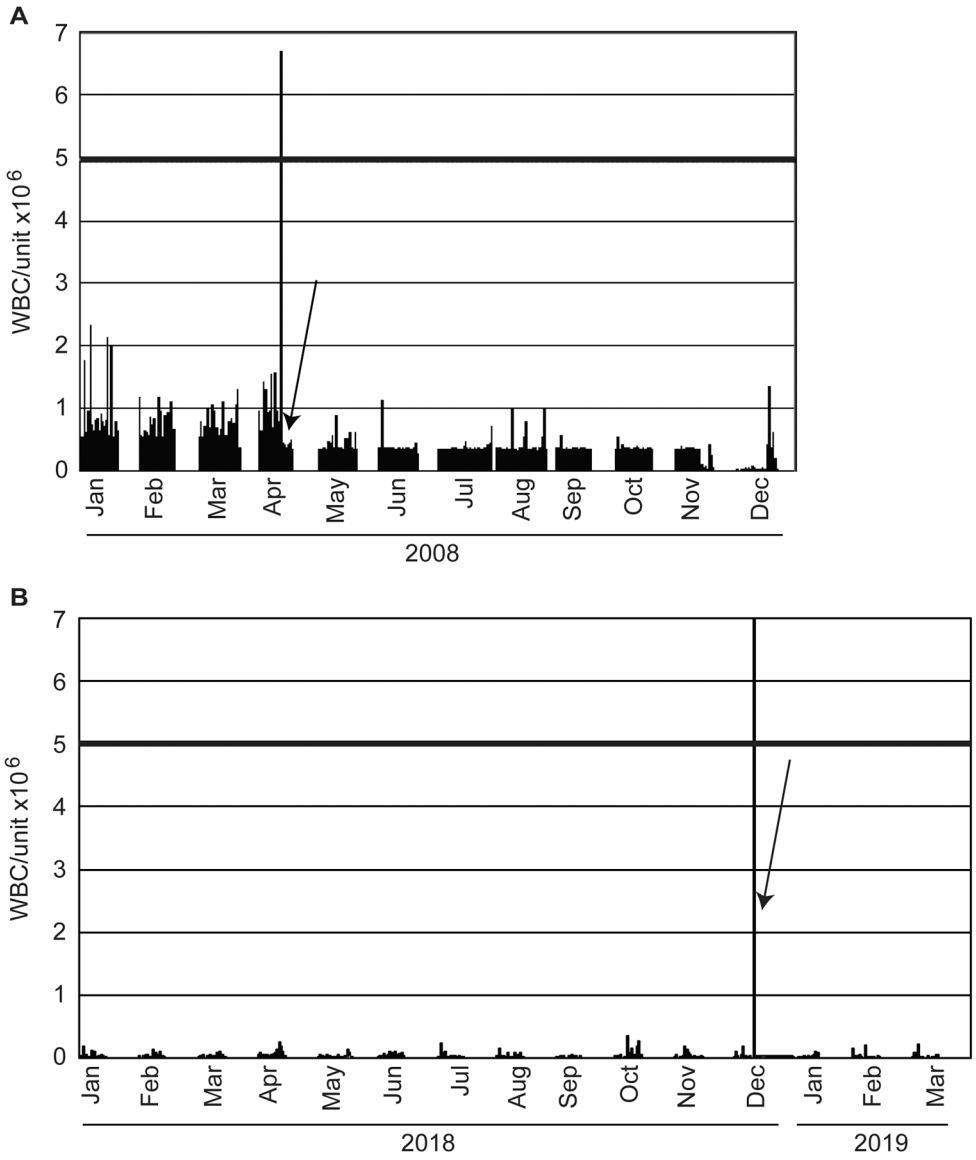

Figure 3. Leukoreduction quality control data.

Plots the number of residual WBCs detected per QC unit by month in (A) 2008 or (B) 2018/2019 at BloodSource (now Vitalant). The arrow in (A) indicates a change in leukoreduction practice from the Fenwal whole blood in-line LR filter system, in which units were leukoreduced prior to centrifugation, to the Fenwal Flex Excel “spin first” system, in which RBCs and plasma are first separated by centrifugation, followed by leukoreduction of the RBCs. The arrow in (B) indicates a filter failure.

Table 1.

Characteristics of enrolled patients with initial and follow-up evaluation for TA-MC

Characteristics	Non-transfused (N=54)	Transfused (N=324)	P-value
Age, years, mean ± SD	40 ± 15	42 ± 19	0.35
Male sex, n (%)	38 (70)	243 (75)	0.47
Blunt mechanism of injury, n (%)	45 (83)	256 (79)	0.46
Transfer from another hospital, n (%)	13 (24)	82 (25)	0.85
Initial systolic blood pressure upon arrival <90 mm Hg, n (%)	2 (4)	53 (16)	0.024
Injury Severity Score, mean ± SD	15 ± 8	21 ± 12	0.0002
AIS Head score, median (IQR)	2 (0, 3)	2 (0, 3)	0.80
AIS Face score, median (IQR)	0 (0, 0)	0 (0, 0)	0.54
AIS Chest score, mean ± SD	0 (0, 3)	2 (0, 3)	0.18
AIS Abdomen score, mean ± SD	0 (0, 2)	0 (0, 2)	0.050
AIS Extremity score, mean ± SD	1.5 (0, 2)	3 (0, 3)	0 0001
AIS External score, mean ± SD	0 (0, 0)	0 (0, 1)	0.0014
Time from ED arrival to initial sample collection, minutes, median (IQR)	11 (6, 17)	11 (6, 20)	0.25
Packed red blood cell transfusion, units, mean ± SD	—	10 ± 12	—
Packed red blood cell transfusion units, median (IQR)	—	6 (3, 12)	—
Packed red blood cell transfusion units within 48 hours of presentation, median (IQR)	—	2 (1, 7)	—
Time from ED arrival to initial transfusion,* hours, median (IQR)	—	9 (0.8, 45)	—
Plasma transfusion units, median (IQR)	0 (0, 0)	1 (0, 3)	<0.0001
Plateletpheresis transfusion units, median (IQR)	—	0 (0, 1)	—
Cryoprecipitate transfusion units, median (IQR)	—	0 (0, 0)	—

* The “time of initial transfusion” is defined as the time of issue of the first transfused unit of packed red blood cells from the hospital blood bank to the patient’s bedside.

Table 2.

Microchimerism levels in this and previous studies

Study (w/cite.)	Patient Pop (n)	Time-Frame (Dates of Tx)	Blood Processing	WBC counts (per unit)	Rates of MC, n (%)		
					Any	Short-Term	Long-Term
PROMC[13]	*Trauma (378 transfused, 206 long-term‡)	12/02/06–07/31/10	†Leukoreduced	<1×10^6	21 (6.8)	24 (6.5)	1 (0.5)
TRIPS[10]	§Adult & Pediatric, Female (409)	2001–2009	**Leukoreduced, some gamma irradiated		12 (3)	12 (3)	0 (0)
Veterans[5]	††Combat-Injured Veterans (163)	1939–1975	Whole blood	~5×10^9	16 (9.8)	NT	16 (9.8)
Seattle[8,24]	‡‡Trauma (67)	02/03/03–08/30/04	§§Total		22 (32.8)	NT	22 (32.8)
			Leukoreduced Non-LR	****<1×10^6 or ~5×10^9*	*13 (37.1)*	*NT*	*13 (37.1)*
					9 (28.1)	*NT*	*9 (28.1)*
UCD[4,6,20,23]	*Trauma (63, 27 long-term[3])	09/18/00–02/2002	Total		40 (63.5)	40 (63.5)	7/27 (25.9)
			Leukoreduced†††(13)		*7 (53.8)*	*7 (53.8)*	*2/7 (28.6)*
			Non-LR (50)		*33 (66)*	*33 (66)*	*5/20 (25)*

*UC Davis Medical Center

†In 2006 BloodSource used the Fenwal whole blood in-line LR filter system. Units were filtered first as refrigerated CPD whole blood, and then spun to create the packed cells and plasma. Adsol was added to the RBCs and stored. Beginning on August 18, 2006, BloodSource increased the spin time on the centrifugation step to obtain more recovered plasma. Beginning on April 28, 2008, BloodSource implemented the Fenwal Flex Excel "spin first" system to make RBC and plasma from CPD whole blood. Adsol is then added to the RBC and then leukocyte reduced by "soft-sided" Flex Excel filter at refrigeration temperatures. The filter is "soft sided" so it can be centrifuged with the CPD whole blood. We did not see a significant difference in microchimerism rates between these 2 time periods.

‡Samples collected ≥180 days after transfusion

§The National Institutes of Health (NIH) Clinical Center and The NIH Heart Center at Suburban Hospital, Bethesda, Maryland. Pediatric patients were enrolled at Children's National Medical Center (CNMC), Washington, DC.

**Prestorage leukoreduced blood components: all RBCs and PLTs transfused to adults were gamma irradiated (minimum of 25 Gy), children received irradiated cellular blood components only for specific indications.

††WWII, Korea, and Vietnam wars.

‡‡Harborview Medical Center

§§Puget Sound Blood Center: Whole blood was collected into a Terumo Teruflex 500 mL blood bag containing 70 mL citrate-phosphate-dextrose anticoagulant. The red cell units were isolated by centrifugation and preserved in AS-5 solution (Optisol). Red cells were leukoreduced within 24 hours of collection using the Leukotrap SCRC Leukocyte Reduction Filtration System with a high efficiency Pall BPF4 filter (Pall, East Hills, NY).

***Leukoreduced cell units met routine quality control requirements of having <5×10^6 white blood cells/unit with 90% of units having <1×10^6 leukocytes/unit.

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†††Pall doc-on filter used after the red cells are created