Male-only fresh-frozen plasma for transfusion-related acute lung injury prevention: before-and-after comparative cohort study

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BACKGROUND: Transfusion-related acute lung injury (TRALI) is one of the most serious complications of blood transfusion. It can be caused by incompatible white blood cell antibodies in transfused plasma. The objective of this study was to quantify the reduction of TRALI after introduction of male-only plasma for transfusion as a preventive measure, which took effect in 2007.

STUDY DESIGN AND METHODS: In the Netherlands all cases of TRALI are reported to the national hemovigilance office. All reported cases of TRALI from 2002 to November 2009 were considered for inclusion. Those meeting the Canadian consensus clinical definition were included and subdivided according to whether or not the patient had received quarantine fresh-frozen plasma (Q-FFP) in the 6-hour period before the reaction. The numbers of TRALI cases involving plasma donated before the measure and of those involving plasma donated after the measure were compared to TRALI cases that did not involve Q-FFP to adjust for reporting bias.

RESULTS: A total of 110 cases were included in the analysis. Of 68 cases before the measure, 36 involved Q-FFP. Thirty-one cases occurred after the measure of which eight involved Q-FFP. Eleven occurred in the transitional period, of which four involved Q-FFP. The population-attributable risk of premeasure plasma among TRALI cases occurring before the measure was 0.33 (95% confidence interval, 0.09-0.51).

CONCLUSIONS: In the Netherlands the male-only Q-FFP measure was associated with a 33% reduction of TRALI cases.

Transfusion-related acute lung injury (TRALI) is one of the most serious transfusion reactions and one of the top three causes of transfusion-related mortality in most hemovigilance registries.[1,2] According to the Canadian consensus criteria, respiratory distress, hypoxia, increased airway resistance, and frothy sputum in ventilated patients arise within 6 hours of transfusion and are associated with (new) infiltrates showing on X-ray. This is assumed to be due to neutrophils entering the pulmonary interstitium and fluid loss into the alveoli.[3,4] TRALI has been attributed to incompatibility between donor white blood cell (WBC) antibodies (HLA Class I and II antibodies as well as granulocyte antibodies) in transfused plasma and recipient

ABBREVIATIONS: Q-FFP = quarantine fresh-frozen plasma; PAR = population-attributable risk; TRIP = Transfusion Reactions in Patients.

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Data were collected and assessed by or under the supervision of JCW-O, EAB, AvT, PZ, and MRS; AB also assessed the reports. The analysis was designed and performed by RAM, JCW-O, and JGvdB. JCW-O drafted the article and is the guarantor. All authors critically reviewed the article, agreed to the decision to submit it for publication and had access to the data.

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WBCs.[5,6] However, in many cases no WBC incompatibility is found. In the postulated two-hit mechanism of TRALI, a first hit consists of neutrophil priming or initial triggering of endothelium in the pulmonary vascular bed. The second hit can be the transfusion of WBC antibodies incompatible with the recipient or other factors that arise during storage of blood products.[4]

The proportion of TRALI cases that are deemed to be caused by WBC incompatibility has been estimated at up to 89%.[3] WBC antibodies are mainly induced by pregnancy or blood transfusion.[7] Therefore several countries where fresh-frozen plasma (FFP) is used for transfusion have introduced FFP preferentially or exclusively derived from male donors who have never received a blood transfusion with the aim to reduce the number of TRALI cases. In the United Kingdom, analysis of 10 years of TRALI registration within "SHOT" (Serious Hazards of Transfusion), the national hemovigilance office, shows that implementation of preferential male-only FFP has led to a near disappearance of TRALI associated with WBC incompatibility after plasma transfusion.[2] However, this may be partly a consequence of the SHOT method of assessing "imputability," the likelihood that the clinical picture of TRALI is related to transfusion. SHOT grades imputability of TRALI reports higher in the presence of patient-incompatible WBC antibodies. The international consensus definition for TRALI does not include WBC incompatibility as a criterion.[8,9]

The male-only measure became effective in the Netherlands for all quarantine FFP (Q-FFP; henceforth in this article we will refer simply to "plasma") distributed to hospitals since July 1, 2007. The aim of this study was to quantify the reduction of TRALI cases, as defined by the international consensus definition, after implementation of male-only plasma.

MATERIALS AND METHODS

Design and study setting

We performed a cohort study among all patients who had a diagnosis of TRALI in the Netherlands from 2002 to 2009 with the aim of comparing the incidence of TRALI before and after the male-only plasma measure became effective. In the Netherlands all suspected cases of TRALI are reported to TRIP (Transfusion Reactions in Patients), the national hemovigilance system that became fully operational in 2003. The reports are submitted on a paper or digital reporting form; additional information is requested from hospitals if necessary for standardized classification. TRIP also receives information on reported TRALI cases from the blood service. Inclusion was terminated on November 15, 2009, when a further measure was introduced in the production of platelet (PLT) concentrates.

Patients

TRALI case definition

TRALI cases had to conform to the criteria of the international consensus definition of TRALI: a patient was included in the cohort if there were clinical findings of hypoxia with bilateral infiltrates on the chest X-ray, starting within 6 hours of the transfusion of a labile blood component; circulatory overload had to be excluded as a (more likely) cause.[8,9] Information on the clinical condition of the patient was evaluated for known risk factors for acute lung injury (ALI) or other possible causes of hypoxia with a temporal relationship to the respiratory distress.

All reports were reviewed by a panel of transfusion experts and assessed on clinical information without considering results of WBC serologic investigation, which in most cases were not available to the reviewing committee. If the patient had a risk factor for ALI (e.g., aspiration, toxic inhalation, lung contusion, near drowning, cardiopulmonary bypass, pneumonia, acute pancreatitis, sepsis), the case was flagged as a "possible TRALI" according to the consensus definition.[8,9] Cases were excluded if there were other more likely causes for the respiratory problems. All blood components received by the patient up to 6 hours before onset of respiratory symptoms were recorded.

Transfusional setting and analysis periods

In the Netherlands plasma for transfusion is prepared from apheresis plasma, which is released after the donor has been retested for infectious diseases after a minimum of 6 months. From October 2006 all plasma collected for Q-FFP and from July 2007 onward all plasma distributed to the hospitals was from male never-transfused donors. Units distributed before July 1, 2007, were not recalled from the hospitals and were transfused from the hospital inventory over the following months. Cryosupernatant plasma is occasionally used for refractory thrombotic thrombocytopenic purpura and prepared on demand from Q-FFP.

Since 1988 all PLT products and since 2002 all red blood cell (RBC) components have been leukoreduced by prestorage filtration ($<1 \times 10^6$ WBCs per unit). Plasma for transfusion meets the same specification. RBCs are stored in SAGM additive solution (AS) and contain less than 20 mL of residual donor plasma. More than 90% of PLT concentrates are prepared from five pooled buffy coats and resuspended in either 200 mL of plasma from one of the donors (approx. 70% of total PLT units) or PLT AS with residual approximately 85 to 100 mL of plasma consisting of less than 20 mL of plasma from each buffy coat. Apheresis PLTs are collected in a volume of 150 to 400 mL of donor plasma and are used for special indications such as HLA-matched PLTs or parvovirus B19- or cytomegalovirus-safe products. During the study years the

total number of blood components distributed to the hospitals annually was approximately 700,000 units.

For TRALI cases reported after July 2007 the donation date of transfused plasma was checked. Reports where any plasma had been transfused were classified according to the donation date of the plasma as occurring with products from before or after the measure. TRALI cases involving no plasma were assigned to the same period as any plasma-associated TRALI in that month. The three analysis periods were before the measure (2002-June 2007), the transitional period during which cases were associated with plasma both from before and from after the measure (July-November 2007), and after the measure (December 2007-November 15, 2009). Plasma-associated cases during the transitional period were assigned according to the date of donation of the plasma and the cases without plasma were assigned half to before and half to after the male-only measure for purposes of calculation.

Statistical analysis

We compared the number of reported TRALI cases from before introduction of the male-only measure with the number after it had become effective. If the measure was effective a reduction will be seen in the number of TRALI patients who received one or more units of plasma, with or without other blood components, when only male plasma was available for transfusion. The number of reported cases where the patient had not been transfused with plasma reflects the overall sensitivity of TRALI detection and reporting in any period. This number was used to correct for changes in this sensitivity.

We expected that after the measure became effective there would be a drop in the proportion of TRALI reports after transfusion of plasma against the total number of reported TRALI cases. The decrease represents the population-attributable risk (PAR) for female plasma as available before the measure and corresponds to the fraction of TRALI prevented by the implementation of male-only plasma. An additional sensitivity analysis was performed, calculating the PAR separately for the ramp-up phase of reporting to TRIP (2002-2004) and for the plateau phase (from 2005-mid 2007). The main result was recalculated with the omission of reports from the interim period as an additional verification.

The formula used is as follows:

$$\mathrm{PAR} = (R - R_0)/R = 1 - \text{risk after}/\text{risk before},$$

with R the risk of TRALI in transfusion recipients before the measure and R_0 the risk in transfusion recipients after the measure.

During the reporting period there was little change in numbers of blood components distributed in the Netherlands,[10] so stable proportions of patients transfused with different types and combinations of types of blood component are assumed. The number of TRALI reactions (N) reported in a given period is

$$N = X \times f \times Y,$$

in which X is the "true" incidence rate of TRALI reactions (number per year), f is the proportion detected and reported, and Y is the follow-up period (years).

$$\begin{aligned}\mathrm{PAR} &= 1 - (\text{risk after}/\text{risk before}) = 1 - X_A/X_B \\ &= 1 - (N_A/(Y_A \times f_A))/(N_B/(Y_B \times f_B)).\end{aligned}$$

For TRALI reactions where no plasma was transfused, the "true" rate cannot have changed since the measure was introduced so

$$X_{B,\text{no plasma}} = X_{A,\text{no plasma}}.$$

Since we collected TRALI reactions with and without plasma concurrently, we can also assume that f at any time is the same for TRALI with and without plasma. This allows the proportion $Y_A \times f_A/(Y_B \times f_B)$ (for all cases) to be estimated by $N_{A,\text{ no plasma}}/N_{B,\text{ no plasma}}$. Thus the PAR was calculated as

$$\mathrm{PAR} = 1 - ((N_A/N_B) \times (N_{B,\text{no plasma}}/N_{A,\text{no plasma}}))$$

simply using the observed numbers of reported TRALIs.

A confidence interval (CI) for the PAR was calculated using

$$\mathrm{Var}(\ln[1 - \mathrm{PAR}]) = 1/N_{B,\text{no plasma}} - 1/N_B + 1/N_{A,\text{no plasma}} - 1/N_A.$$[11]

RESULTS

Characteristics of the study population

The study population comprised 110 patients with TRALI approved by expert review as complying with the TRALI definition. Figure 1 shows the numbers of all suspected TRALI reactions per year from 2002 to 2009 according to the types of blood component(s) received by the patient.

TRALI before and after the male-only plasma measure

The earliest TRALI involving one or more plasma units from after the measure occurred in July 2007, the last case where one or more plasma units dated from before the measure occurred in November 2007. Thirty-one of the TRALI cases were designated as possible TRALI according to the consensus definition because one or more other risk factors for ALI were present.

Outcomes and estimation

The annual number of reports of TRALI rose for all types of blood component between 2002 and 2007, which can be

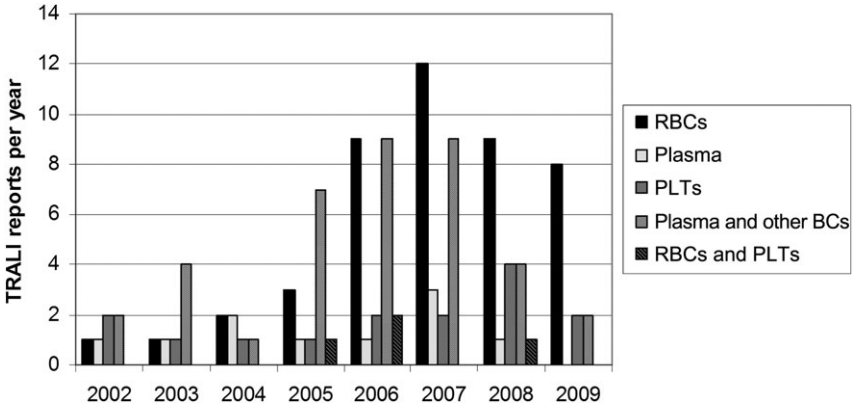

Fig. 1. Reports of suspected TRALI and associated blood components, 2002 through 2009. BCs = blood component(s).

attributed to increased awareness of TRALI. The initial increase in total annual number of reports to the new hemovigilance reporting system had leveled off in 2005. A total of 68 cases of TRALI occurred before the male-only plasma measure, of which 36 involved plasma, with or without other types of blood components. From December 2007 there were 31 cases, of which eight involved plasma. Four of the 11 cases in the transitional period were associated with plasma, two with plasma donated before the measure. Table 1 summarizes the numbers of reports with and without plasma per analysis period. The overall PAR was 0.33 (95% CI, 0.09%-0.51%) for all TRALI. After exclusion of possible TRALI it was 0.37 (0.06-0.58). In the sensitivity analysis comparing the separate periods of 2002 through 2004 and 2005 through mid-2007 to that after the measure the PAR was comparable although with a wider CI: PAR 0.41 (95% CI, 0.07-0.67); and 0.31 (–0.02 to 0.54), respectively.

DISCUSSION

The male-only plasma measure was associated with a 33% reduction of TRALI in the Netherlands, a reduction totally driven by lower numbers of cases where plasma had been transfused in combination with RBCs and/or PLTs. The finding implies that against the mean number of approximately 20 reports per year before the measure, some seven of the previously reported cases annually may have been avoided by the measure. Moreover, since the plasma measure can only prevent TRALI caused by plasma, this size of effect means that the majority of TRALI cases where plasma had been transfused before the measure were in fact caused by female plasma. The figures in Table 1 show that TRALI cases where plasma had been transfused are in the majority in the period before the measure and that this is reversed after the measure.

We observed a higher attributable risk when cases of possible TRALI were excluded. In some cases where other risk factors for ALI were present, ALI was probably not induced by the transfusion. Inclusion of some such cases leads to dilution and underestimation of the effect of the measure. The higher attributable risk after exclusion of possible TRALI is probably more valid and provides further support that there is a true reduction.

Strengths and limitations

The strength of this analysis lies in its inclusion of all reported patients meeting the standardized criteria for TRALI in a whole country, with as little as possible interference from awareness of the results of WBC serology testing. Reporting of such a serious complication as TRALI to TRIP and/or the blood service is expected to be nearly complete. An important advantage is that we use the number of TRALIs not associated with plasma to correct for variability in detection and reporting behavior. The fact that a similar effect is found in the sensitivity analyses of the subperiods supports our use of these cases as a comparator.

A limitation of the study is its observational nature and reliance on spontaneous reporting of cases. A recent analysis has shown that bias may operate in the decision whether to report a reaction as suspected TRALI.[12] If any interpretation bias operated it could be expected to favor reports of TRALI associated with FFP and to have most strongly influenced TRALI reactions where FFP was the sole product transfused. However, these findings do not support this. Also, since most clinicians in the Netherlands are not aware of the plasma measure, this reporting preference is unlikely to have changed and therefore could not have biased our analyses.

The overall blood use and the proportions of type of blood component remained largely stable over the study period, except for a slight (less than 10%) decrease in the number of both RBC and plasma units distributed to the hospitals between 2002 and 2004 (see Table 2). Thus a relative reduction of the use of plasma compared to cellular blood components has not contributed to a lower incidence of TRALI. The assumption of unchanged risk associated with RBC and PLT transfusion could also be challenged if female plasma donors returned to whole blood donation. In fact, however, female donors continued to donate plasma for fractionation.

The overall incidence of reported TRALI appears to show a downward trend after the year 2007 (Fig. 1). Analyses by TRIP show that there have been increased reports of transfusion-associated circulatory overload and other transfusion reactions, suggesting that the diagnosis of TRALI is assigned more critically.[1] As explained above the

TABLE 1. TRALI cases and transfused blood components per analysis period

TRALI	Before the measure, January 1, 2002-July 1, 2007	Transitional period,* July 1, 2007-December 1, 2007	After the measure, December 1, 2007-November 15, 2009	Total	PAR = 1 – ((N_A/N_B) × (N_B, no plasma /N_A, no plasma))
All TRALI	68	11	31	110	1 – ((36.5/73.5) × (35.5/26.5)) = 0.33 (95% CI, 0.09-0.51)
With plasma	36	2 before 2 after	8	48	
Without plasma	32	7	23	62	
TRALI, excluding cases of possible TRALI	48	8	23	79	1 – ((27/52) × (22.5/18.5)) = 0.37 (95% CI, 0.06-0.58)
With plasma	28	2 before 1 after	7	38	
Without plasma	20	5	16	41	

* If cases in the interim period are left out of the calculation the PAR becomes 1 – ((31/68) × (32/23)) = 0.37 (0.12 – 0.54) and 0.40 (0.08 – 0.61) excluding possible TRALI.

TABLE 2. Annual blood use (to nearest 1000) and rate of reported TRALI

Blood components distributed (to nearest 1000 units)					
Year	RBCs	Plasma	PLTs	Total number of TRALI and overall rate per 100,000 units distributed	
2002	630	105	50	6	0.76
2003	617	112	48	7	0.90
2004	585	97	53	6	0.81
2005	568	92	51	13	1.83
2006	556	92	51	23	3.29
2007	555	93	54	26	3.71
2008	554	98	51	19	2.70
2009	564	90	49	12	1.70

calculated drop in TRALI is based on the ratio of TRALI cases where plasma was (one of blood components) transfused, to cases without plasma, and would be valid despite a reduced trend in the overall level of TRALI detection and reporting.

Consistency with prior findings

A reduction by 33% is slightly higher but in the same order of magnitude as suggested by the findings of WBC serology as reported recently from our country.[13] The reduction is comparable to observational pre- and postintervention data on ALI in ruptured abdominal aneurysm repair from a single UK center (0.39; 95% CI, 0.16-0.90).[14] An American study of TRALI fatalities in 2003 to 2005 found that 18 of 38 probable TRALI fatalities (47%) were associated with female antibody-positive FFP and might be avoided by limiting transfusion of WBC antibody-containing FFP.[15] This proportion is again similar although the relative contribution of alloimmune-mediated TRALI associated with FFP would not necessarily be the same among cases with fatal outcome. A recent overview of probable TRALI (including nonfatal cases) reported by the American Red Cross describes a decrease from 30 cases associated with plasma transfusion in 2006 to 10 cases in 2008 after implementation of male-predominant plasma for transfusion.[16]

In the UK reports to SHOT of TRALI-associated with FFP containing patient-incompatible WBC-reactive antibodies decreased from 10 in 2003 to none in 2004 through 2007 since implementation of preferential use of male plasma. This suggests that, if supply of exclusively male plasma is achieved, this measure could prevent most or all TRALI caused by plasma. As explained above, SHOT assesses the likelihood that a suspected TRALI is indeed transfusion-related partly on the basis of the finding of concordant HLA antibodies in the transfused unit(s). The overall rate of reported TRALI (assessed as highly likely, probable, or possible) before the change in the United Kingdom was 1.9 per 100,000 units, compared with 2.6 per 100,000 in 2005 through 2006 in our registry. In the Netherlands, the expert assessors were blinded to the results of this investigation from 2007 onward. Before that year they were not consistently blind to the results but these were not used for the clinical definition of TRALI. The calculated reduction in the Netherlands is remarkably similar to the effect in the UK despite the important difference in the assessment of cases; this is in line with the hypothesis of TRALI cases having being prevented by elimination of patient exposure to incompatible WBC antibodies in plasma from female donors.

Meaning of the study and implications for clinicians and policymakers

Not in all countries are donors excluded if they have been recipients of transfusion. Plasma from male donors who have (ever) been transfused should logically also be excluded, although it has been established that

pregnancy-related HLA antibodies persist for longer than antibodies developed after blood transfusion. In the Netherlands it was possible to implement the measures for no significant costs and without serious threat to the blood (plasma) supply. We adopted the use of male-only plasma for the plasma added to PLT pools in mid-November 2009. A further safety improvement will be obtained if this achieves a comparable risk reduction for the PLT concentrates preserved in plasma.

Some blood services have implemented antibody screening for all female donors, with repetition of the screening after pregnancy.[17] This should have comparable efficiency in preventing TRALI, while resulting in fewer donor deferrals, but is associated with increased costs. Other countries (e.g., France, Ireland, Norway, Finland) use pooled solvent/detergent virally inactivated plasma and report that TRALI is not seen in association with this product. Reduction in noninfectious transfusion complications (both TRALI and allergic reactions) was included as an important aspect in a recent review of cost-effectiveness aspects of this product.[18]

In conclusion, our findings suggest that in the Netherlands the male-only plasma measure has led to a reduction of TRALI cases of approximately 33%.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest relevant to the manuscript.

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