Role of Riboflavin- and UV Light-Treated Plasma in Prevention of Transfusion-Related Acute Lung Injury

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Keywords

Riboflavin · UV light · Plasma · TRALI

Summary

Introduction: Risk reduction strategies for transfusion-related acute lung injury (TRALI) include the preferential use of male donors to provide fresh frozen plasma (FFP). Implementing this measure based on FFP quarantine program is a very complex process. To improve FFP inventory management and the availability of FFP from male donors, the Mirasol Pathogen Reduction Technology® (PRT) system for FFP using riboflavin and UV light was adopted in our region in 2012. **Methods:** The percentage of male/female FFP units issued and TRALI cases in patients receiving FFP in the period before implementing riboflavin and UV light (2010–2011) was compared with the period post implementation of riboflavin and UV light (2012–2013). **Results:** In 2010 and 2011, there was one FFP transfusion-related TRALI case reported per year, when the proportion of male/female FFP distributed to the hospitals was 60/40. During 2012 and 2013, there have been no FFP transfusion-related TRALI cases, when the proportion of male/female FFP distributed to the hospitals was around 97/3. Mirasol PRT allows quick availability (24 h from collection) compared to quarantined FFP (≥3 months from collection). **Conclusion:** Thanks to its readiness, simplicity and feasibility, riboflavin- and UV light-treated FFP implementation can facilitate the preferential use of FFP from male donors as a TRALI prevention strategy.

Introduction

The Mirasol Pathogen Reduction Technology® (PRT) system for platelets (PLTs) and plasma uses riboflavin and UV light in order to oxidize nucleic acids (DNA or RNA) through electron transfer reactions, resulting in the inhibition of pathogen genome and leukocyte replication which leads to inactivation [1, 2]. Since riboflavin is an essential nutritive ingredient that is normally present in the human body and as its photo-products are non-toxic, there is no need for their removal from inactivated blood components [3, 4].

Since 1995, the Balearic Islands Blood Bank (BIBB) has maintained a fresh frozen plasma (FFP) quarantine program to provide plasma for transfusion therapy of patients within our community. Basically, the system consists in releasing the plasma unit once a donor has been retested by NAT for HIV, HBV HCV, with negative results after a period of at least 3 months [5].

In 2011, the National Committee for Blood Safety established a recommendation for the preferential use of male donors to provide FFP as a strategy to prevent transfusion-related acute lung injury (TRALI). Selecting FFP from male donors to be quarantined is a very complex process due to multiple manual steps in the quarantine program. In addition, the plasma units are usually unavailable for issue for at least 3 months. As a result, in 2012, the BIBB initiated the routine use of FFP derived from whole blood donations prepared using riboflavin and UV light for the transfusion support of patients with congenital and acquired coagulopathies. However, the quarantine program for plasmapheresis donations was still maintained to provide plasma transfusion support to patients with thrombotic thrombocytopenic purpura (TTP) since the superior efficacy of quarantined FFP (qFFP) compared to inactivated plasma has previously been demonstrated for TTP treatment, and specifically with plasma treated with methylene blue [6,7].

Table 1. Percentage of qFFP and PRT-FFP units distributed to the hospitals from 2010 to 2013

	Pre-riboflavin and UV light FFP period		Post-riboflavin and UV light FFP period		p value
	2010	2011	2012	2013	
Total FFP	5,583	4,803	5,584	5,538	0.223
PRT-FFP*	167 (3%)	144 (3%)	1,563 (28%)	1,548 (28%)	<0.001
qFFP	5,416 (97%)	4,659 (97%)	4,021 (72%)	3,990 (72%)	0.056
*From 2010 to 2011, PRT-FFP consisted of FFP inactivated with methylene blue. From 2012 to 2013, PRT-FFP consisted of FFP inactivated with riboflavin and UV light.					

Another important reason for selecting riboflavin and UV light PRT for FFP was that this technology can also be applied to PLTs. In fact, we have recently implemented riboflavin and UV light PRT for PLTs.

This study presents TRALI annual incidence in our region related to the use of riboflavin- and UV light-treated FFP from 2012 to 2013, and compares the results with those of the period from 2010 to 2011 prior to the introduction of riboflavin and UV light technology for FFP in our community.

Material and Methods

Hemovigilance Data Collection

The BIBB collects and supplies all blood components for 15 public and private hospitals, which altogether provide more than 3,500 beds in a region with a population of about 1 million inhabitants. The BIBB performs approximately 42,000 whole-blood and 5,000 PLT component collections per year to support transfusion therapy for diverse patient populations, including those cared for by hematology-oncology and cardiovascular surgery specialists. Around 12,530 l of plasma are obtained after fractionation: 11,102 l (88.6%) are used by the plasma fractionation industry to make albumin and immunoglobulins and 1,428 l (11.4%) are destined for transfusion.

The Balearic Island Hemovigilance Division (BIHVD) located in the BIBB facility, one of the 17 regional hemovigilance divisions in the Spanish Hemovigilance Network, collects and analyses all serious transfusion events reported by the Balearic Island Medical Centers. The BIHVD represents the autonomic level of the Spanish Hemovigilance Network in our region; therefore, it is responsible for communications between the Community Medical Centers and the Spanish Ministry of Health.

While maintaining patient confidentiality, information regarding serious transfusion event occurrence in our community was obtained from the BIHVD database. The BIHVD system as well as the Spanish Hemovigilance Network meet the requirement of the European Directive 2005/61/EC on Hemovigilance [8] and are based on an anonymous, voluntary, non-punitive serious adverse events reporting program.

The annual incidence of TRALI from 2010 to 2013 was obtained from the BIHVD database.

Preparation of Blood Components

Plasma Components

Quarantine FFP

Since 1995, FFP units derived from whole blood and plasmapheresis donations have been rapidly frozen after processing to -62°C in 1 h using a shock freezer (MP1101 freezer with MicroCascade™, ThermoGenesis Corp, Rancho Cordova, CA, USA), labelled with ISBT 128 quarantine

code, and then stored in the quarantine room at -30°C for up to 2 years. After a minimum of 3 months, if the donor returns to donate and is confirmed seronegative for HIV, HBV, and HCV by NAT testing, the FFP unit is released for quarantine and re-labelled with the ISBT 128 code (information system eProgesa; Mak-System, Paris, France). The released FFP unit is transferred from the quarantine room to the blood component room ready for issue.

Riboflavin- and UV Light-Treated FFP

From 2012 to 2013, plasma units derived from whole blood donations have been inactivated using riboflavin and UV light (Mirasol PRT system; TerumoBCT, Lakewood, CO, USA), according to the manufacturer's instructions, within 2 h after separation and 4–8 h after collection. The inactivation process involves the addition of riboflavin (35 ml; 500 $\mu\text{mol/l}$ in 0.9% saline) to the plasma which has previously been drained into a specific bag as part of a pathogen reduction plasma illumination/storage set. This set is placed into the illuminator and exposed to UV light (6.24 J/ml; 265–370 nm) under linear agitation (120 cycles/min) at a temperature of $<37^{\circ}\text{C}$. The illumination process lasts approximately 6 min. Finally, plasma is transferred to an ISBT-labelled (information system eProgesa) storage bag, and frozen to -75°C in 1 h using a shock freezer (Kryoplasma 44, Angelantoni Industrie SpA, Milan, Italy), and then stored at -30°C immediately after the inactivation procedure.

Data Analysis and Statistical Methods

Data from the BIBB were extracted from the computerized database used to manage the blood inventory. The annual incidence of TRALI, from 2010 to 2013 was obtained from the BIHVD database. Differences between the two observation periods were compared by a two-sample t-test. All reported p values were two-sided, and statistical significance was declared at a p value of less than 0.05.

Results

Hemovigilance Data Related to the Use of Riboflavin- and UV Light-Treated FFP

Riboflavin and UV light PRT treatment of whole blood donation-derived FFP was implemented in our institution in 2012. The qFFP system was also continued to cover plasma treatment for TTP patients. Since 2012, the percentage of FFP distributed to the hospitals has been 72% qFFP and 28% PRT-treated FFP (FFP treated with riboflavin and UV light; Mirasol PRT system). Prior to 2012, the percentage of PRT-treated FFP (FFP inactivated with methylene blue; THERAFLEX MB-Plasma, MacoPharma, Mouvaux, France) was 3% and that of qFFP 97%. Therefore, from 2012 to 2013 the PRT-

Table 2. Percentage of male/female FFP units distributed to the hospital and TRALI cases in patients receiving FFP transfusions from 2010 to 2013.

	Pre-riboflavin and UV light FFP period		Post-riboflavin and UV light FFP period		p value
	2010	2011	2012	2013	
Male FFP, %	51.1	69.7	99.0	94.0	0.032
Female FFP, %	48.9	30.3	1.0	6.0	0.032
TRALI*	1/4,637	1/ 3,569	0/ 4,239	0/ 4,298	
*The cases of TRALI included in this table are related to TRALI associated with FFP transfusions and not related to the transfusion of other blood components, i.e. these are the cases of TRALI per number of FFP units transfused per year in our region.					

treated FFP supply increased from 3% to 28% ($p < 0.001$); however, the number of total FFP units distributed to hospitals over the years shows no statistically significant difference ($p = 0.223$) (table 1).

In 2011 and 2012, prior to the routine implementation of riboflavin and UV light treatment, there was one FFP transfusion-related TRALI case reported per year, when the proportion of male/female FFP distributed to the hospitals was around 60/40. Both TRALI cases were related to the transfusion of qFFP from female donors who presented antibodies against patient's leukocytes.

Although, there was one RBC transfusion-associated TRALI case in 2013, there have been no FFP transfusion-related TRALI cases in our region since 2012, when the proportion of male/female FFP distributed to the hospitals was around 97/3. The percentage of FFP from female donors decreased significantly when comparing the period before implementing riboflavin and UV light inactivation (2010–2011) with that after riboflavin and UV light inactivation (2012–2013) (40% vs 3%, $p = 0.032$) (table 2). FFP from female donors issued in 2012 and 2013 were mainly from AB and B blood groups.

After 2 years of using plasma treated with riboflavin and UV light in the routine, no notification of severe adverse events in patients has been reported in our community. Recently, we have also started using riboflavin and UV light technology for PLTs, with no serious transfusion events reported yet.

Discussion

PRT is associated with increased blood safety through the inactivation of virus, bacteria, and parasites. It also provides an additional means of protecting the blood supply from emerging agents as well as offering further protection against both known and as yet unidentified agents [9]. Other benefits are those derived from the inactivation of leukocytes that are not removed by leukoreduction [10]. Essentially, preventing alloimmunization of leukocyte-borne antigens, and eliminating the risk of transfusion-associated graft-versus-host disease are important advantages of riboflavin- and UV light-based PRT [11–13].

In our community, riboflavin- and UV light-treated FFP was implemented in 2012 in order to preferentially provide plasma from male donors so as to prevent TRALI. Prior to this implementation, there was one FFP transfusion-related TRALI case per year (in 2011 and 2012). However, no cases of FFP transfusion-associated cases of TRALI have been reported in our region since 2012, although there was one RBC transfusion-related case of TRALI reported in 2013. This may be related to the 2012 implementation of the TRALI-preventing strategy of transfusing FFP from male donors rather than due to the introduction of riboflavin- and UV light-treated FFP itself. In fact, the efficacy of excluding plasma products from female donors on decreasing the incidence of TRALI is widely recognized [14–16]. However, it is also worth mentioning that riboflavin- and UV light-based PRT does not induce neutrophil priming in plasma and consequently does not affect acute lung injury caused by stored blood components in a two-event in vivo model [17].

As a result of our experience and the implementation of riboflavin- and UV light-treated FFP, we were able to provide mainly male donor plasma to hospitals, an accomplishment that would otherwise have been extremely difficult using our qFFP program alone. In reality, the riboflavin- and UV light-treated FFP method has considerable advantages over the qFFP system, especially in terms of FFP inventory management.

The qFFP system involves quarantining the donated FFP unit for longer than the HBV, HIV, and HCV window period or until the donor is confirmed seronegative for these transfusion-transmissible viruses. A period of 6 months is generally applied [5]; however, since NAT is performed routinely to all donations in our institution, the quarantine period applied is 3 months.

Selecting plasma to be quarantined from male donors is a very complex process due to multiple manual steps required from collection to storage, and subsequently the plasma units are usually unavailable for issue for at least 3 months. In addition, it is unlikely that the demand for AB and B plasma could be entirely met using only male donor qFFP due to the low frequency of these donors in the general population. However, due to the simplicity and readiness of the riboflavin and UV light method for treating FFP, selecting male donor FFP units for inactivation is easier, and they become available to

be transfused in only 24 h. These two factors contribute to meeting the demand for mainly male donor AB and B FFP units. More importantly, the qFFP system only provides protection against the viruses analyzed (HIV, HBV, and HCV). However, riboflavin- and UV light-based PRT protects against virus, bacteria, parasites, and emerging pathogens.

On the other hand, even though there is a slight loss of coagulation factor activity in riboflavin- and UV light-treated (PRT) plasma, it still fulfils the quality standards required for transfusion [18, 19]. Moreover, it has been demonstrated that even after storage for 1 year at -18°C , riboflavin- and UV light-treated FFP still shows acceptable levels of most coagulation factors [20].

In our institution, the quarantine program for plasmapheresis donations is still maintained to provide plasma transfusion support to patients with TTP. The clinical efficacy of qFFP has previously been demonstrated to be superior to that of methylene blue-inactivated plasma for TTP treatment [6, 7]. Although the safety and feasibility of using riboflavin- and UV light-treated FFP in TTP patients has recently been described [21], prospective studies are required to study the clinical efficacy of riboflavin- and UV light-treated FFP compared to qFFP in TTP patients.

In conclusion, the number of proven cases of TRALI (i.e., where donor antibody and recipient antigen match) associated with FFP transfusions have decreased in our community since the implementation of the preferential use of male donors to provide FFP. The adoption of this risk reduction strategy for TRALI has been possible thanks to the implementation of FFP PRT based on riboflavin and UV light which has notable advantages over the qFFP system, especially in terms of improving FFP inventory management.

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Disclosure Statement

The authors declare that they have no conflicts of interest related to the manuscript submitted to TRANSFUSION MEDICINE AND HEMOTHERAPY.

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