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October 01, 2020

To: Directors of Clinical Laboratories
Directors of Transfusion Services

Subject: **Pathogen Reduced Platelets**

LifeSouth is pleased to introduce **INTERCEPT® Platelets** (psoralen-treated; pathogen-reduced apheresis platelets).

INTERCEPT Platelets are *pathogen reduced* components in which a broad spectrum of clinically relevant pathogens and leukocytes have been inactivated, thus reducing the risk of transfusion-transmitted infections and transfusion-associated graft versus host disease.

This product provides a safe alternative to irradiated/CMV products and addresses residual risks related to sepsis, established pathogens such as HIV, HBV, HCV, and emerging pathogens for which tests do not exist, such as Chikungunya and Dengue viruses.

The FDA has approved this technology to replace bacterial detection testing.

Please refer to the attached retrospective study concerning PRT products in pediatric and neonatal patients; the study shows no significant increase in adverse events or indicators that PRT products are unsafe in pediatric and neonatal patients.

## Product Codes

The following table includes the ISBT component codes currently assigned to pathogen reduced platelets. Your computer system should be able to accept all of these new products.

| | Pathogen Reduced Platelets | Expiry Date |
|---|---|---|
| **E8331V00** | Apheresis PLATELETS\|ACD-A/XX/20-24C\|ResLeu:<5E6\|Psoralen-treated | 5 days |
| **E8332V00** | Apheresis PLATELETS\|ACD-A/XX/20-24C\|ResLeu:<5E6\|1st container\|Psoralen-treated | 5 days |
| **E8333V00** | Apheresis PLATELETS\|ACD-A/XX/20-24C\|ResLeu:<5E6\|2nd container\|Psoralen-treated | 5 days |
| **E8334V00** | Apheresis PLATELETS\|ACD-A/XX/20-24C\|ResLeu:<5E6\|3rd container\|Psoralen-treated | 5 days |
| **E8335V00** | Apheresis PLATELETS\|ACD-A/XX/20-24C\|ResLeu:<5E6\|<3E11 plts\|Psoralen-treated | 5 days |

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Please feel free to contact Lori Masingil, VP of Quality Assurance at 352-224-1679, if you have further questions.

# Use and safety of riboflavin and UV light-treated platelet transfusions in children over a five-year period: focusing on neonates

*Teresa Jimenez-Marco*,[1,2] *Marta Garcia-Recio*,[3,4] *and Enrique Girona-Llobera*[1,2]

**BACKGROUND:** There are very few published reports about the use and safety of pathogen reduction technology (PRT) based on riboflavin and UV light for platelet (PLT) transfusion in children.

**STUDY DESIGN AND METHODS:** A two-part study was conducted: 1) a study investigating the safety of PLTs treated with riboflavin and UV light-PRT transfused to 379 children and 1,980 adults over a 5-year period; 2) an observational study evaluating the efficacy of PLT use in 132 neonates transfused with PRT-treated PLT compared with 99 neonates receiving standard PLTs over two 5-year periods.

**RESULTS:** The rate of adverse reactions related to transfusions with PRT-treated PLTs was found to be slightly higher in adults than in children, although not statistically significant (0.19% vs. 0.12%; p = 0.85). All PLT transfusion events in children were mild. From 2013 to 2017, 379 children received 4,236 riboflavin and UV light-treated PLTs. Hemato-oncology patients received the most PLT transfusions (61.2%), followed by critically ill children in the Pediatric Intensive Care Unit (PICU) (24.6%), and neonates in the Neonatal Intensive Care Unit (NICU) (10.5%). A significant increase in PLT transfusions was found in 132 neonates transfused with 458 PRT-treated PLTs compared with 99 neonates receiving 176 standard PLTs, measuring PLT use/patient (p = 0.031) and total PLT dose/patient (p = 0.041).

**CONCLUSIONS:** Riboflavin and UV light-based PRT for PLTs seems to be safe for children. Neonates required a higher number of PLT transfusions when these were PRT-treated rather than standard. A long-term follow-up for chronically transfused children and randomized clinical trials are needed.

Malignancies are the most common indication for platelet (PLT) transfusion in the pediatric population.[1] The current therapy for childhood cancer is increasingly based on the use of blood products, especially PLTs.[2] The growing demand for hematopoietic stem cell transplantation in pediatric malignancy treatment[3] has concomitant risks of pathogen transfusion transmission and other effects. After recovery, a child has a lifetime ahead for developing complications. In fact, around 70% of pediatric transfusion recipients are long-term survivors and at risk for late transfusion-related adverse events.[1] Despite comprehensive donor selection criteria and considerable advances in pre-transfusion screening tests for infections, the "zero risk" blood transfusion is still far from being achieved, not only in terms of transfusion–transmissible viral infections such as HIV, HBV and HCV,[4] bacterial contamination and sepsis, alloimmunization, febrile and allergic reactions,[5] but also particularly worrisome pediatric transfusion complications such as transfusion-transmitted graft-versus-host disease (GVHD) and cytomegalovirus (CMV) infections.

In efforts to improve transfusion safety, pathogen reduction technologies (PRT) are being implemented.[6] In addition to inactivating bacteria, parasites and viruses, including CMV,[7,8] PRT brings other benefits: replacement of gamma irradiation by white blood cell (WBC) inactivation, which eliminates the risk of transfusion-transmitted GVHD[9]; a lower frequency of febrile and allergic transfusion reactions[10–12] and possibly a reduction

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in alloimmunization and preventing PLT refractoriness,[13,14] which according to a recent publication still needs to be confirmed by evidence from clinical practice.[15]

Different PRTs are currently available for treating PLTs, plasma, red blood cells and whole blood (WB). This study is focused on PLTs treated with riboflavin (vitamin B2) together with UV light in the range of 265-370 nm. (Mirasol PRT). Briefly, after the riboflavin is added to the PLT concentrate, it is activated by UV light to produce free oxygen radicals that irreversibly damage the pathogen nucleic acid and block its proliferation.[6] Since 2013, the Balearic Islands Blood Bank (BIBB) has been using riboflavin and UV light-treated PLTs in transfusion support for adult and pediatric patients with thrombocytopenia. Currently, there are very few published reports on PRT based on riboflavin and UV light for PLT transfusion in the pediatric population.[16,17] With the aim of shedding some light on this field, a two-part study was conducted: 1) a study investigating the safety of riboflavin and UV light-treated PLT transfusions in children compared with adults over a 5-year period (2013-2017); 2) an observational study in neonates evaluating the transfusion efficacy of riboflavin and UV light-treated PLTs compared with standard PLTs over two 5-year periods (2003-2007 vs. 2013-2017).

## MATERIAL AND METHODS

### Study design

The BIBB collects and supplies all blood components for 22 hospitals in the Balearic Islands, which provide a total of 3,675 beds for a population of around one million inhabitants. The BIBB collects around 40,000 WB and 5,700 PLT component donations per year for transfusion therapy in different patient categories, both adults and children, such as oncology, hematology, and medical and surgery conditions, including patients requiring cardiovascular surgery.

In 2013, the BIBB initiated universal routine use of riboflavin and UV light-treated PLTs (Mirasol). From January 2013 through December 2017, 28,657 PLT components consisting of 12,982 pooled buffy coat PLTs and 15,675 apheresis PLTs were produced. All the PLT products made during this period (28,657 PLT concentrates) were treated with riboflavin and UV light PRT to provide PLT transfusion support to all patients from the Balearic Islands.

The Balearic Islands University Hospital, the largest in the region, is comprehensively equipped with medical and surgical departments. It has the largest hemato-oncology service in the region, including the main bone marrow transplant and pediatric hemato-oncology units. Around 60% of all PLT transfusions and 95% of all pediatric PLT transfusions in the Balearic Islands are performed in this hospital. For these reasons, the Balearic Islands University Hospital was chosen for a retrospective analysis of the use and safety of riboflavin and UV light-treated PLT transfusions in children with thrombocytopenia.

### Patient information

The safety of riboflavin and UV light-treated PLT transfusions in children with respect to adults was studied over a 5-year period (2013-2017). In accordance with the hospital ethics committee, PLT use data were analyzed for 379 children up to 15 years of age, who received 4,236 PLTs treated with riboflavin and UV light between 2013 and 2017 at the Balearic Islands University Hospital. Likewise, data from 1,980 adults transfused with 13,367 riboflavin and UV light-treated PLTs between 2013 and 2017 were also reviewed. Information on PLT transfusion safety was obtained from the Balearic Island Hemovigilance system (BIHVS). According to the European Directive on Hemovigilance,[18] in Spain, as in other European Community member countries, it is compulsory to report serious transfusion events in medical centers to the health care authorities. The BIHVS is completely integrated into the Spanish Hemovigilance System. Mild and moderate transfusion events, which are all those not defined as serious adverse reactions by the European Directive,[18] such as fever and allergy reactions not associated with inpatient hospitalization or prolongation of hospitalization attributable to the adverse reaction, persistent or significant disability, life-threatening evolution or death, are also reported to the BIHVS.

Additionally, to evaluate the efficacy of riboflavin and UV light-treated PLT transfusion in neonates, data from 99 neonates receiving 176 standard PLTs (diluted in 100% plasma and non-PRT-treated) during a 5-year control period from 2003 to 2007 were compared with those of 132 neonates transfused with 458 riboflavin and UV light-treated PLTs diluted in PAS from 2013 to 2017. The two study periods were chosen because in the years 2008-2012 the blood bank temporarily used an alternative PRT to treat PLTs (not based on riboflavin and UV light).

### Collection and preparation of riboflavin and UV light-treated PLTs

From January 2013 to December 2017, 28,657 PLT components—12,982 pooled buffy coat PLTs and 15,675 apheresis PLTs—were prepared with PAS-E (Terumo-PLT Additive Solution + [T-PAS+]) in a ratio of 35% plasma and 65% PAS. Pooled buffy coat PLT components, which represented 45% of the PLT production, were prepared using the COMPOMAT G4 automatic blood component processing system (Fresenius Kabi) and the automatic TACSI system (Terumo BCT). Likewise, 55% of apheresis PLTs were obtained using three automatic cellular separators (Amicus, Fresenius Kabi; Trima, Terumo BCT; and Haemonetics MCS +, Haemonetics Corp.). All 28,657 PLT components were treated with Mirasol PRT (Terumo BCT), according to the manufacturer's instructions. The PRT-treatment was carried out within the first 22 hours post-collection. The PLT concentrates were transferred into an illumination/storage bag and riboflavin solution was added (35 $\pm$ 5 mL). The PLT units were then placed in the illuminator and exposed to UV light for 5 to 7 minutes with light energy in the range of 265-370 nm.


**Fig. 1. Collection of adult apheresis doses and splitting into pediatric doses.**

PLTs intended for pediatric transfusions were obtained from split single-donor apheresis concentrates (Fig. 1). The use of a single PRT treatment kit to produce multiple pediatric doses, also historically utilized for untreated products, is cost-effective and practical. For children weighing below 15 kg, an adult PLT apheresis donation (300 mL, mean PLT yield post-PRT $3.2 \times 10^{11}$/U) was aliquoted into four pediatric PLT units (75 mL, mean PLT yield post- PRT $0.8 \times 10^{11}$/U) using the transfer bag system Compoflex (Fresenius Kabi). For children weighing more than 15 kg, an adult PLT apheresis donation (300 mL, mean PLT yield post- PRT $3.2 \times 10^{11}$/U) was available for transfusion.

In accordance with the national requirements, 75% of adult PLT units should have a PLT yield $\geq 3 \times 10^{11}$/U and 75% of pediatric PLT units should have a PLT yield $\geq 0.5 \times 10^{11}$/U.[19] Therefore, the PLT target dose was increased to $3.5 \times 10^{11}$/U after the implementation of PRT to compensate for the expected 5% PLT loss in the transfer step of the riboflavin/UV light PRT procedure.[20] These requirements were consistently fulfilled, given that the mean PLT yield for PLT apheresis post-PRT was $3.2 \times 10^{11}$/U and the mean PLT yield post-PRT per pediatric aliquot was $0.8 \times 10^{11}$/U.

Riboflavin and UV light-PRT was used instead of gamma irradiation to meet specific patient indication requirements. PRT-treated PLTs were stored for up to 7 days. All PLTs were pre-storage leukoreduced in accordance with National and European requirements (residual WBC content below $10^6$ per unit in >90% of production).[19,21] (Table 1).

The riboflavin and UV light PRT for PLT apheresis workflow was designed as follows (Fig. 2): firstly, the PLT apheresis units were PRT-treated, after a 2 hours resting period and before 22 hr post-collection, early in the morning on post-collection Day 1, while the infectious disease and immunohematology testing was performed in the laboratory. Secondly, after the testing was done, at 2 pm at Day 1 post-collection, the PRT-treated PLT apheresis units were aliquoted in four small units on demand, and they were ready for hospital distribution at around 3 pm at Day 1 post-collection.

Over the 5-year PRT period, from 2013 to 2017, all PLT transfusions for adult and pediatric patients carried out in the Balearic Islands were treated with riboflavin and UV light. Indications for PLT transfusion in children were based on the guidelines for transfusion in fetuses, neonates, and older children. Basically, a PLT count of $10 \times 10^9$/L was used as a transfusion trigger in non-infected stable children but higher thresholds were used for children who were bleeding and/or unstable.[22] For transfusing neonates and children from 1 year of age and <15 kg, aliquoted pediatric PLT units (75 mL) were used at a transfusion PLT dose of 10-20 mL/kg and transfusion rate of 10-20 mL/kg/h. Thus, the same child could be

**TABLE 1. Variables of 28,657 PLT components diluted in PAS and treated with riboflavin and UV-light from 2013 to 2017**

| Total PLT production (n = 28,657) | Riboflavin and UV-light PLT production in a 5-year period (2013-2017) |
|---|---|
| **Buffy coat PLTs (n = 12,982)** | PLTs intended for adult transfusions |
| **45% PLT production** | |
| Platform | TACSI |
| Whole blood (mL) | 450 ± 45 |
| Anticoagulant | CPDA |
| PLT target dose ($\times 10^{11}$) | 3.5 |
| Mean PLT yield post-PRT ($\times 10^{11}$) ± SD | 3.08 ± 0.08 |
| Pool size | 5 |
| Plasma target (%) | 35 |
| PAS (%) | 65 |
| **Apheresis PLTs (n = 15,675)** | PLTs intended for adult and pediatric transfusions |
| **55% PLT production** | |
| Platform | Trima, Amicus, MCS+ |
| Anticoagulant | ACD-A |
| PLT target dose ($\times 10^{11}$) | 3.5 |
| (Mean ± SD) PLT yield post-PRT ($\times 10^{11}$) | 3.2 ± 0.23 |
| (Mean ± SD) pediatric PLT yield post-PRT($\times 10^{11}$) | 0.8 ± 0.05 |
| Plasma target | 35 |
| PAS (%) | 65 |
| PLT storage time (days) | 7 |
| Pre-storage universal leukoreduction | Residual WBC content below $10^6$ per unit in >90% of production |

transfused with PLTs from the same apheresis donor on four different occasions within a week (storage time for PRT-PLTs is 7 days), if required, consequently reducing donor exposure fourfold. For children >15 kg, a single PLT concentrate was available for transfusion at the transfusion rate of 10-20 mL/kg/h, which does not imply the transfusion of the whole PLT concentrate (300 mL), but the volume needed, according to the transfusion dose of 10-20 mL/kg. Furthermore, to avoid over-transfusion of blood components, at the Balearic Islands University Hospital all prescriptions for pediatric patients are ordered and prescribed in milliliters (mL) rather than PLT concentrates.

### Data analysis and statistical methods

BIBB data were extracted from the computerized database used to manage the blood component inventory. Information on child and adult blood transfusion reactions associated with PLT transfusions was obtained from the BIHVS, while preserving patient confidentiality. Transfusion information for the Balearic Islands University Hospital was obtained from the hospital's computerized database, in accordance with the hospital ethics committee. Values for all continuous variables were summarized as mean and standard deviations. Differences in mean values between the two series of observations were compared by a two-sample t test. All p values reported were two-sided, and significance was determined at a p value of less than 0.05.

## RESULTS

### Riboflavin and UV light-treated PLT use in children

Included in the study were 379 children up to 15 years of age who received 4,236 riboflavin and UV light-treated PLTs at the Balearic Islands University Hospital from 2013 to 2017. Out of these 379 children, 132 were neonates. The number of PLTs used per child was calculated based on the number of children who received PLTs and the total number of PLTs transfused. The total PLT dose/patient ($\times 10^{11}$) was calculated by multiplying the pediatric PLT content (PLT transfusion dose) by the number of PLT concentrates used per patient. Patients were classified according to the clinical service providing medical or surgery care and ordering PLT transfusions.

Pediatric PLT transfusions were given predominantly to hemato-oncology patients (61.2%), followed by critically ill children admitted in the Pediatric Intensive Care Unit (PICU) (24.6%), and neonates in the Neonatal Intensive Care Unit (NICU) (10.5%). The mean number of PLT concentrates and the total dose of PLTs received per patient were highest for these three patient groups in the same descending order. Patients receiving the highest number of PLT transfusions belonged to the allogeneic or autologous bone marrow transplant subgroup of the pediatric hemato-oncology group (Table 2).

### Riboflavin and UV light-treated PLT transfusion efficacy evaluated in neonates

PLT transfusion efficacy was evaluated by comparing PLT use in 99 neonates receiving 176 standard PLTs between 2003 and 2007 and 132 neonates transfused with 458 PLTs diluted in PAS and treated with riboflavin and UV light between 2013 and 2017.

The standard PLTs used during the period 2003 to 2007 consisted of pediatric PLT units obtained from aliquoted PLT apheresis donations, diluted in 100% plasma and non-PRT-treated. Each pediatric standard PLT aliquot contained

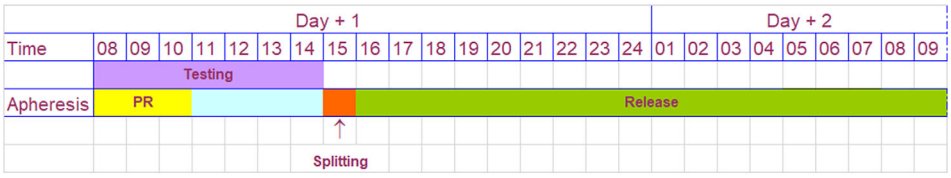


**Fig. 2. Riboflavin/UV light PRT for platelet (PLT) apheresis workflow.**

**TABLE 2. PLT use in children transfused with PAS-PLTs treated with riboflavin and UV light in 2013-2017 at the Balearic Islands University Hospital**

| Pediatric patients transfused with riboflavin and UV light-treated PLTs during 2013-2017 at the Balearic Islands University Hospital | Number of PLT transfusions | Number of PLT concentrates used per patient Mean (±SD) | Total PLT dose/patient ($\times 10^{11}$) Mean (±SD)† |
|---|---|---|---|
| **Total (n = 379; 100%)** | **4,236** | **6.6 (±2.8)** | **5.3 (±2.5)** |
| Critically ill neonates in the NICU (n = 120; 31.7%) | 445 (10.5%) | 3.9 (±1.5) | 3.3 (±1.3) |
| Neonates (n = 12; 3.2%) | 13 (0.3%) | 0.8 (±0.5) | 0.7 (±0.4) |
| Critically ill children in the PICU (n = 77; 20.3%) | 1,044 (24.6%) | 11.5 (±6.2) | 9.4 (±5.6) |
| Hemato-oncology pediatric patients (n = 123; 32.5%) | 2,590 (61.2%) | 19.8 (±7.7) | 15.7 (±6.8) |
| *Allogeneic bone marrow transplants (2 acute lymphoblastic leukemias) 2 (1.6%)** | *44 (1.7%)* | *22* | *17.6* |
| *Autologous bone marrow transplants (1 acute myeloblastic leukemia, 3 neuroblastomas, 1 Ewing's sarcoma) 5 (4.1%)** | *177 (6.9%)* | *35.4* | *28.32* |
| Children with medical conditions (n = 44;11.6%) | 140 (3.3%) | 3.2 (±0.4) | 2.2 (±0.3) |
| Children undergoing surgery (n = 3;0.7%) | 4 (0.1%) | 0.5 (±0.7) | 0.4 (±0.6) |

* The number of children receiving an allogeneic or autologous bone marrow transplant has been included in the overall number of hemato-oncology pediatric patients.

† The total PLT dose/patient ($\times 10^{11}$) was calculated by multiplying the pediatric PLT content of transfused components ($0.8 \pm 0.05 \times 10^{11}$ for riboflavin and UV light-treated PLTs) by the number of PLT concentrates used per patient.

a mean of $0.8 \times 10^{11}$ PLTs/U, i.e., a similar amount to the pediatric aliquot from PLT apheresis donations, diluted in in a ratio of 35% plasma and 65% PAS and treated with riboflavin and UV light, used during the period 2013 to 2017.

There was a statistically significant increase in PLT usage in neonates transfused with PLTs diluted in PAS and treated with riboflavin and UV light compared with neonates receiving standard PLTs, measuring PLT use per patient (p = 0.031) and total PLT dose per patient (p = 0.041) (Table 3).

## Safety of PLTs diluted in PAS and treated with riboflavin and UV light in adults and children from 2013 to 2017

Approximately 60% of the PLT transfusions performed annually in the Balearic archipelago are carried out at the Balearic Islands University Hospital. From 2013 to 2017, a total of 2,359 adult and child patients in this hospital received 17,603 PLT transfusions treated with riboflavin and UV light; i.e., 1,980 adults were transfused with 13,367 PLTs and 379 children up to 15 years of age received 4,236 PLTs. Therefore, 83.3% of patients transfused with PLTs were adults and 16.7% were children, receiving 75.9% and 24.1% of the PLT transfusions, respectively. Among these patients, 26 PRT-treated PLT transfusion adverse reactions in adults and 5 in children were reported over the five-year period, according to BIHVS data based on the voluntary and anonymous notification of transfusion-related adverse reactions. In each patient population, the percentage of adverse reactions after transfusion with PLTs diluted in PAS and treated with riboflavin and UV light-PRT was similar: 26 reactions in 1,980 adults (1.31%) and 5 reactions in 379 children (1.32%) (p = 0.90). The rate of total transfusion reactions related to the number of PRT-treated PLT transfusions in adults was slightly higher than those in children but not statistically significant: 26 reactions reported for 13,367

**TABLE 3. Comparison of PLT use in neonates transfused with standard PLTs from 2003 to 2007 with neonates transfused with PAS-PLTs treated with riboflavin and UV light from 2013 to 2017 at the Balearic Islands University Hospital**

| Neonate patients receiving PLTs either during 2003 to 2007 or 2013 to 2017 | Number of PLT transfusions | Number of PLT concentrates used per patient Mean (±SD) | Total PLT dose/patient ($\times 10^{11}$) Mean (±SD)† |
|---|---|---|---|
| Neonates transfused with standard PLTs from 2003 to 2007 at the Balearic Islands University Hospital (**n = 99**)* | 176 | 1.8 (±0.3) | 1.6 (±0.3) |
| Neonates transfused with riboflavin and UV light-treated PLTs from 2013 to 2017 at the Balearic Islands University Hospital (**n = 132**)† | 458 | 3.6 (±1.3) | 2.9 (±1.2) |
| p value | 0.001 | 0.031 | 0.041 |

* The standard PLTs consisted of pediatric PLT units obtained from aliquoted plateletapheresis donations, diluted in 100% plasma and non-riboflavin and UV light-treated.

† The riboflavin and UV light PLTs consisted of pediatric PLT units obtained from aliquoted plateletapheresis donations, diluted in a ratio of 35% plasma and 65% PAS and treated with riboflavin and UV light. Both PLTs, standard and PRT-treated, contained the same PLT amount, i.e., a mean of $0.8 \times 10^{11}$ PLTs/U.

**TABLE 4. Comparison of transfusion adverse reactions between adults and children transfused with PAS-PLTs treated with riboflavin and UV light from 2013 to 2017**

| AR with riboflavin and UV light-treated PLTs from 2013 to 2017 | Adults | Children | |
|---|---|---|---|
| Number of PLTs transfused | **13,367** | **4,236** | |
| Number of patients receiving PLTs | **1,980** | **379** | **p value** |
| Febrile reactions (n; %) | 13 (50%) | 1 (20%) | |
| % Febrile reactions/patients | 0.66 | 0.26 | NS |
| % Febrile reactions/PLT transfusions | 0.10 | 0.02 | NS |
| Allergic reactions (n; %) | 11 (42%) | 4 (80%) | |
| % Allergic reactions /patients | 0.56 | 1.06 | NS |
| % Allergic reactions/PLT transfusions | 0.08 | 0.09 | NS |
| TACO (n; %)* | 2 (8%) | 0 (0%) | |
| TACO/patients | 0.10 | 0 | NS |
| TACO/PLT transfusions | 0.01 | 0 | NS |
| Total (n) | **26** | **5** | |
| % AR/patients† | **1.31%** | **1.32%** | **NS** |
| % AR/PLT transfusions | **0.19%** | **0.12%** | **NS** |

* TACO = Transfusion-associated circulatory overload.
† AR = adverse reaction.
NS = not significant.

transfusions given to adults (0.19%) and 5 reactions reported for 4,236 transfusions administrated to children (0.12%) (p = 0.85). The percentage of allergic reactions with respect to the total number of transfusion reactions was twice as high in children (80%) as in adult patients (42%). However, when considering the allergic reactions rate related to the number of patients transfused (adults 0.56 vs. children 1.06; p = 0.3) and the number of PLTs transfused (adults 0.08 vs. children 0.09; p = 0.42), the difference between adults and children is not statistically significant (Table 4).

In general, most reactions were mild, except for an allergic reaction suffered by an adult patient who developed respiratory complications requiring admission in the ICU.

There have been no reported cases of PLT bacterial contamination, sepsis, transfusion-transmitted GVHD and CMV infections or other severe transfusion-related reactions since the BIHVS was initiated in 2003. In the period 2013 to 2017, all adverse transfusion reactions observed in children transfused with PAS-PLTs treated with riboflavin and UV light were mild, such as febrile non-hemolytic and mild allergic reactions.

## DISCUSSION

The results reported here are in line with the epidemiological findings related to pediatric standard PLT transfusions in the literature.[1,2,23] Pediatric patients with hemato-oncology malignancies were the predominant recipients of PLTs diluted in PAS and treated with riboflavin and UV light-PRT (61.2%), followed by critically ill children admitted in the PICU (24.6%), and neonates in the NICU (10.5%). It is well-known that pediatric cancer patients undergoing chemotherapy or allogeneic or autologous hematopoietic stem cell transplantations are at high risk of bleeding and represent the pediatric patient group who receive the most PLT transfusions.[3]

Out of 379 children included in the study (2013-2017), 132 were neonates. The efficacy of PAS-PLTs treated with riboflavin and UV light-PRT was evaluated in the neonate group by comparison with a control group. Our results show that the neonates transfused with PRT-treated PLTs had higher PLT transfusion requirements than the neonates receiving standard PLTs. To the best of our knowledge, this is the longest series of neonatal patients to be included in a study of transfusions with riboflavin and UV light treated-PLTs. The only previous report describing the use of such PRT-treated-PLTs in children included only 51 pediatric patients (age range: 0.4-18 years; mean: 11 years) transfused with 141 riboflavin and UV light treated-PLTs and 86 controls (age range: 0.4-18 years; mean 11 years) transfused with 291 standard PLTs. These authors found that the CCI at 1 to 4 hours and at 18 to 24 hours were significantly higher in the control group, although both groups reached clinically effective CCI.[16]

Clinical trials of blood components, mainly focused on adult populations, have demonstrated that the transfusion of PRT-treated PLTs is commonly associated with a lower post-transfusion increase in PLT count.[24] Some studies, supported by systematic meta-analyses, have shown the hemostatic efficacy of PRT-treated PLTs to be similar to that of standard non-PRT-treated PLTs.[24–26] In fact, the few trials including children have found comparable rates of clinically significant bleeding and mortality in children transfused with standard or PRT-treated PLTs, although some studies report a higher PLT transfusion requirement in the latter.[24,27] Given the few published reports of using PRT-treated PLT transfusions in pediatric patients, ongoing post-market surveillance of clinical safety and efficacy or PRT blood components in children is undoubtedly needed.[28]

In a recently published retrospective and observational study assessing the efficacy and safety of Food and Drug Administration (FDA)-approved PRT-treated PLTs in children, standard and PRT-treated PLTs were found to have similar usage rates. However, a small statistically significant increase in PLT requirement was observed with PRT-treated PLT transfusion in children aged 1 to 18 years but not in NICU patients or in infants 0 to 1 year not in the NICU.[29] Conversely, our study demonstrates that neonates transfused with riboflavin and UV light-treated PLTs (a PRT system different from the one evaluated by the FDA[29]) have a higher PLT transfusion need that those receiving standard PLTs.

Interestingly, the riboflavin and UV light-PRT system is currently being evaluated in a phase III clinical trial in the US (Identifier: NCT02964325). The results of this promising trial will help to shed light on the safety and efficacy of riboflavin and UV light-treated PLT transfusions in the pediatric population.[30]

It is important to note that all PLT concentrates produced by the BBIB have been pre-storage leukoreduced since 2000,

stored in PLT additive solution (PAS) since 2008, and treated with riboflavin and UV light-PRT since 2013. Since the implementation of PRT, the PLT concentrates have not been treated with gamma irradiation. The inactivation of WBC prevents transfusion-transmitted GVHD,[9] while pre-storage leukoreduction[31] and PRT avoid transfusion-transmitted CMV infections.[8] No cases of transfusion-transmitted GVHD or transfusion-transmitted CMV infections in children have been reported in the Balearic Islands since our hemovigilance transfusion reaction reporting system (BIHVS) was initiated in 2003.

In our study, the rate of adverse reactions related to transfusions with PLTs diluted in PAS and treated with riboflavin and UV light-PRT was found to be slightly higher in adults than in children, although the difference was not statistically significant. In contrast, a recent study analyzing pediatric adverse reactions to non-PRT-treated blood component transfusions reported that the rate of reactions per PLT transfusion in the pediatric group was double the adult reaction rate, and that children presented higher rates of allergic, febrile non-hemolytic and acute hemolytic reactions than adult patients.[32] Similarly, according to the 2017 SHOT report, the most common transfusion reactions in children are PLT reactions, mainly allergic, whereas in adults RBC transfusion reactions predominate.[5]

We found that the percentage of allergic reactions with respect to the total number of PLT transfusion reactions was twice as high in children (80%) as in adult patients (42%). However, when considering the allergic reactions rate related to the number of patients transfused (adults 0.56 vs. children 1.06; $p = 0.3$) and the number of PLTs transfused (adults 0.08 vs. children 0.09; $p = 0.42$), the difference between adults and children is not statistically significant.

Our results differ from previous reports on non-PRT-treated blood component transfusions[5] as in our study the ratio of overall adverse reactions to PRT-treated PLT transfusion was not statistically different between children and adults. This difference is likely because our patients were transfused with PLTs diluted in PAS and treated with riboflavin and UV light, as both factors can reduce the incidence of reactions. Recent hemovigilance studies have reported that the use of riboflavin and UV light-treated PLTs has the potential to decrease the rate of transfusion reactions, specifically febrile non-hemolytic and allergic reactions.[10–12] It is also known that PLTs suspended in PAS are associated with a lower rate of febrile non-hemolytic and allergic reactions than PLTs stored in 100% plasma.[33]

Additionally, a retrospective study on the efficacy and safety of riboflavin and UV light-PRT-treated PLTs in pediatric cancer patients found a low rate of transfusion-related adverse events that was not significantly different from the control group transfused with non-PRT-treated PLT.[16] Therefore, riboflavin and UV light PRT together with PLT storage in PAS can apparently reduce the rate of febrile and allergic reactions to PLT transfusions in children. Our group has recently demonstrated that the transfusion of PAS-PLTs treated with riboflavin and UV light significantly decreases the rate of febrile and allergic transfusion reactions in adults.[10] Furthermore, all PLT transfusion reactions observed in children were mild from 2013-2017.

A limitation of this preliminary study is that only one control group was used to evaluate the transfusion of PAS-PLTs treated with riboflavin and UV light, i.e, the neonate group transfused with standard PLTs from 2003 to 2007, and PLT usage in other pediatric groups was not assessed. However, taking into account the few published reports on the use of riboflavin and UV light-treated PLT transfusions in children, we believe that our study provides valuable information in this field, since it includes the longest series of newborns transfused with PAS-PLTs treated with riboflavin and UV light to be studied so far.

In conclusion, the results reported here on the usage of PLTs diluted in PAS and treated with riboflavin and UV light-PRT in children are in accordance with the epidemiological data described in other studies on standard PLTs.[1,2,23] The pediatric group receiving the most PLT transfusions were hemato-oncology patients, followed by critically ill children admitted in the PICU, and neonates in the NICU. Our comparative study shows that neonates transfused with PLTs diluted in PAS and treated with riboflavin and UV light-PRT require the transfusion of more PLTs than neonates receiving standard PLTs. Additionally, the adverse transfusion reaction rate in children transfused with PAS-PLTs treated with riboflavin and UV light was found to be in accordance with data in the literature for children[16] and adults[10] receiving PLTs treated with the same PRT. PRT-treated PLTs seem to be safe for children, since in 5 years (2013-2017) not a single severe PLT transfusion reaction was reported in children transfused with riboflavin and UV light-treated PLTs.

However, a long-term follow-up in chronically transfused pediatric patients and clinical trials on riboflavin and UV light-PRT and other PRT systems are needed to support the safe use of PRT-treated PLTs in children.

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## CONFLICT OF INTEREST

The authors have disclosed no conflicts of interest.

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