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Blood transfusions and adverse acute events: a retrospective study from 214 transfusion-dependent pediatric patients comparing transfused blood components by apheresis or by whole blood

Maria Rosaria De Pascale[1*#], Angela Belsito[1*], Linda Sommese[2], Simona Signoriello[3], Antonio Sorriento[4], Maria Vasco[1], Concetta Schiano[5], Carmela Fiorito[1], Giuseppe Durevole[1], Marina Casale[6], Silverio Perrotta[6], Fiorina Casale[6], Roberto Alfano[7], Giuditta Benincasa[5], Giovanni Francesco Nicoletti[8] and Claudio Napoli[5]

[1]*UOC Divisione di Immunologia Clinica, Immunoematologia, Medicina Trasfusionale e Immunologia dei Trapianti, Dipartimento di Medicina Interna e Specialistica, Azienda Ospedaliera Universitaria, Università degli Studi della Campania "Luigi Vanvitelli", Naples, Italy*
[2]*UOC Divisione di Immunologia Clinica, Immunoematologia, Medicina Trasfusionale e Immunologia dei Trapianti, Dipartimento di Medicina Sperimentale, Azienda Ospedaliera Universitaria, Università degli Studi della Campania "Luigi Vanvitelli", Naples, Italy*
[3]*Dipartimento di Salute Mentale e Medicina Preventiva, Statistica, Università degli Studi della Campania "Luigi Vanvitelli", Naples, Italy*
[4]*AORN dei Colli – Ospedale "Monaldi", Naples, Italy*
[5]*Dipartimento di Scienze Cliniche e Chirurgiche Avanzate, Università degli Studi della Campania "Luigi Vanvitelli", Naples, Italy*
[6]*Dipartimento della Donna, del Bambino e di Chirurgia Generale e Specialistica, Azienda Ospedaliera Universitaria, Università degli Studi della Campania "Luigi Vanvitelli", Naples, Italy*
[7]*Dipartimento di Scienze Mediche, Chirurgiche, Neurologiche, Metaboliche e Geriatriche, Università degli Studi della Campania "Luigi Vanvitelli", Naples, Italy*
[8]*Dipartimento Multidisciplinare di Specialità Medico Chirurgiche ed Odontoiatriche, Università degli Studi della Campania "Luigi Vanvitelli", Naples, Italy*
**Equal contribution*
[#]Present address Ospedale "Cardarelli", Naples, Italy

Abstract

Introduction. Blood transfusion is a lifesaving procedure for patients affected by hematological diseases or hemorrhage risk.

Aim. This retrospective study was aimed to evaluate clinical safety of pediatric transfusions by comparing the frequency of adverse events caused by apheretic blood components *vs* whole blood.

Methods. From 2011 to 2015, 214 patients (blood malignancy patients, n = 144 and thalassemic patients, n = 70) received 12 531 units of blood components. The adverse acute reactions occurred during patient hospitalization were reported to the Hemovigilance system and assessed by fitting a logistic mixed-effect model.

Results. A total of 33 (0.3%) adverse acute events occurred. Odds ratio (OR) of adverse events from apheresis *vs* whole blood transfusion adjusted by patient classification was not statistically significant (OR [95% CI], 0.75 [0.23-2.47]).

Conclusion. Our findings showed no significant differences in the prevalence of adverse acute events between blood component collected by apheresis *vs* whole blood in our study center.

Key words

- apheresis
- whole blood
- acute adverse transfusion reactions
- pediatric patients

Address for correspondence: Giuditta Benincasa, Dipartimento di Scienze Cliniche e Chirurgiche Avanzate, Università degli Studi della Campania "Luigi Vanvitelli", Piazza Miraglia 2, 80138 Naples, Italy. E-mail: Dr.benincasa.giuditta@gmail.com.

INTRODUCTION

Blood transfusion is a lifesaving therapy for patients affected by anemia, coagulation disorders, bone marrow aplasia, as well as many other conditions compromising oxygen transport and hemostatic function [1-3]. Despite the increasing of transfusion safety achieved by both application of good manufacturing practice (GMP) and appropriate therapeutic protocols, blood components can be associated with acute (< 24 h) or delayed (≥ 24 h) adverse effects, especially in transfusion-dependent pediatric patients [2].

Acute or delayed adverse effects are classified as immunological and non immunological reactions. Acute adverse events include hemolytic, febrile non hemolytic, allergic and anaphylactic reactions, as well as lung injury, infection or sepsis, and circulatory overload. Delayed adverse events include erythrocyte and platelet alloimmunization, hemolytic reactions, post-transfusion purpura, immunomodulation, graft *versus* host disease, as well as iron overload in long-term transfusion [4, 5]. When acute reactions occur, it is necessary to stop the transfusion procedure to establish an appropriate treatment. Besides, the event must be notify to Blood Bank [4, 5]. Laboratory parameters include hemoglobinemia (pink or red serum/plasma), hemoglobinuria, positive direct anti-globulin test (DAT), elevated indirect and direct bilirubin test, and red blood cell (RBC) abnormalities, such as schistocytes in intravascular hemolysis or spherocytes in extravascular hemolysis [4, 5].

According to the Italian Report of Haemovigilance (2016), from January 1st to December 31st 2016, 1958 adverse reactions were notified in recipients of allogeneic blood components (one every 1560 transfused units); taking into account only adverse reactions that are probably or certainly imputable with a high level of severity the frequency is one every 339 543 transfused units. It is estimated a more than double incidence of transfusion-related adverse acute events in pediatric than adult patients (538 *vs* 252 per 100 000 transfusions) showing a higher frequency of allergic, febrile non hemolytic, and hypotensive reactions [1, 6]. The most frequent side effects in pediatric population are of acute type, including both mild allergic reactions (urticarial, cutaneous) and mild respiratory symptoms [6, 7]. In 2016, the most frequently notified reactions were febrile non-haemolytic reactions (39.2%) and allergic manifestations with only mucosal and cutaneous symptoms (29%), representing about 68.2% of all notified adverse reactions in recipients [8]. In particular, these adverse acute events are mainly associated with platelet (PLT) transfusions followed by RBC and plasma transfusions [6, 7]. The morbidity of blood components requires extreme concern in transfusion practice based on the clinical profiles. Greater efforts should be aimed to administer the lowest dose of blood components, thus avoiding both unnecessary multiple donor exposures and prophylactic transfusions. Moreover, clinicians should evaluate every therapeutic opportunity to reduce blood transfusion-related risk, such as infection and allo-immunization [6, 10]. In this context, patient blood management (PBM) programs are designed to reduce the use of transfusions also through intraoperative, preoperative postoperative strategies aimed at limiting the use of allogeneic components. The PBM programs are well established and implemented in the adult environment and it should be necessary pediatric PBM goal directed protocols even more restrictive than those for adults [9].

Nowadays, infection is still a critical issue because current screening methods are not still able to cover the window period and discriminate the plethora of emerging pathogens [10, 11]. The screening of blood donors using well standardized and highly sensitive laboratory assays has significantly increased the safety of blood transfusion [10]. Indeed, in developed countries, the current risk is very low for a number of known viruses (e.g. HIV, HBV, HCV) which can be detected accurately in the donor blood and lower than the risk related to non-infectious acute blood transfusion reactions (e.g. TACO, TRALI, etc.) [10]. However, emerging pathogens could represent a risk for recipients, including hepatitis E virus (HEV) that is increasing in European countries with a significant variability among the different geographical areas [10]. In this regard, it could be useful the application of new pathogen reduction technologies (PRTs) to improve clinical patient outcome; however, there are some limitations: 1) PRTs are not available for all blood components; 2) current commercial PRTs are not equally effective on all the pathogens; 3) some detrimental alterations have been found in PRTs treated blood components [12]. Besides, efficacy, type and cost of side effects, as well as sanitary policy should be better analyzed, thus allowing the Blood Bank to set up all the possible strategies aimed to improve the transfusion medicine safety, particularly in pediatric population [9, 13-16]. Transfusion reactions in pediatric populations have not been well explored; however, a study evaluating 126 pediatric patients reported a percentage of 14.4% of acute transfusion reaction to PLT transfusion [8]. Generally, donation by apheresis procedures are correlated with fewer adverse events [16].

In light of this, we report our single-center experience focused on a retrospective analyses aimed to evaluate putative difference between apheresis and whole blood transfusions underlying adverse acute events in 214 pediatric patients.

MATERIALS AND METHODS

Study population

From 2011 to 2015, blood components, collected at the Division of Clinical Immunology, Immunohematology and Transfusion Medicine, were transfused in patients with blood malignancy or thalassemia in the Pediatric Department, at Università degli Studi della Campania "Luigi Vanvitelli", Naples, Italy. Pediatric patients (n = 214, aged from 8 to 19 years) received randomized blood components obtained by apheresis or by whole blood, according to the availability in the Blood Bank. Exclusion criteria were the presence of pre-existing cardiopulmonary affections and medical history of allergy and anaphylaxis. Detailed forms on the type and rate of transfusion related to adverse events occurred during hospitalization were obtained

from Pediatric Division and sent mandatorily to our Division for the Hemovigilance Network. The number and the type of blood components transfused under normal clinical practice were obtained from our electronic database. A transfusion reaction was an adverse acute event attributable to a blood product infusion (PLTs, RBCs, plasma). Data on all adverse acute events were registered using authorized and approved procedures. Guidelines on assessing donor suitability for blood donation are reported on DM November 2, 2015 by Italian Minister of Health (www.gazzettaufficiale.it/eli/id/2015/12/28/15A09709/sg) and according to the Society of Transfusion Medicine and Immunohematology (www.centronazionalesangue.it/sites/default/files/it_standards_transf_med.pdf) [17]. Donors were deferred in presence of risk behavior, cardiac pathologies, autoimmune and neoplastic diseases and the use of particular drugs according to Italian legislation.

Blood derivates

Blood donation was performed by apheresis or by whole blood. During the apheresis procedure, the donor is connected through a single venous access to a sterile disposable kit in a closed circuit. The apheresis allowed the collection of aliquots of RBCs, PLTs and plasma using Haemonetics MCS+ 9000 system blood cell separator (Haemonetics S.A. Signy Centre, Ruedes Flèchères 6, Svizzera). The main advantage of this procedure is the low extracorporeal volume (calculated by volume of the apheresis chamber, the hematocrit (Hct) and total blood volume of the donor), which avoids modifications in donor pressure. Through the centrifugal force, blood cell separators collect blood aliquots during the discontinuous flow procedure throughout the programs for the multicomponent collections of RBCs (erytro-apheresis, EA, 947F) and RBCs-plasma (erythro-plasmapheresis, EPA, 947F) and PLTs-plasma (platelet-plasmapheresis, PLT-A, 994EF) while the remaining part is returned to the donor. The circuit used is sterile and disposable while donor extracorporeal part is anticoagulated by using a citrate solution. For EPA/EA, RBCs target yields were programmed to 230-280 g of absolute RBCs (leukodepleted) and 450 mL of plasma. After collection, 70-80 g saline-adenine-glucose-mannitol preservative solution was automatically added to RBCs and the filtration was performed routinely after the last return cycle by gravity through the integrated filters for leukodepletion. RBCs were stored at 4 °C for 42 days. For PLT-A, platelet target yields were programmed to range 2.5-3.5 $\times 10^{11}$ of PLTs and 450 mL of plasma. After collection, PLTs were re-suspended in 130-150 mL of SSP solution (Macopharma, Italy) and automatically filtrated according to the current legislation for leukodepletion. PLTs were stored at room temperature on continuous shaker for up to 5 days [18-21]. By apheresis, 400-650 mL of plasma was collected (DM November 2, 2015 by Italian Minister of Health (www.gazzettaufficiale.it/eli/id/2015/12/28/15A09709/sg) and according to the Society of Transfusion Medicine and Immunohematology (www.centronazionalesangue.it/sites/default/files/it_standards_transf_med.pdf) [17].

Blood bags were handled to avoid any bacterial contamination in the blood product collected. Blood products (PLTs and RBCs) were subjected to periodic and randomized checks for microcontaminations [11, 17]. Whole blood was processed within 8 hours after donation to obtained platelet concentrates (PC), fresh frozen plasma (FFP), packed RBCs (EC), and leukodepleted RBCs (EL) by using a closed system collected in citrate-phosphate-double dextrose. RBC target yields were programmed equal to be at least 280 mL of leukodepleted RBCs with a Hct level of 0.50-0.70% and plasma is collected with a volume ranging from 400 mL to 730 mL.

Statistical analysis

Continuous variables were reported as either mean and standard deviation (SD) or median and interquartile range (IQRs) according to their distribution, as assessed by the Shapiro-Wilk test and compared with t-test or Wilcoxon-Mann-Whitney test. Categorical variables were reported as absolute numbers and percentages and compared with Pearson's chi-square test or Fisher's exact test as indicated. Rate of adverse events were calculated as number of events divided by number of transfusion and compared between transfusion procedures. The effect of transfusion procedures on adverse event was assessed by fitting a logistic mixed-effects model [22]. An unstructured within-subject covariance matrix was used in the analysis (i.e. variances and covariance were allowed to vary at each observation point). Transfusion procedures according to the classification of patients (blood malignancies and thalassemic pediatric patients) were first tested; if the interaction was statistically significant at 0.05 level (i.e., there was enough evidence that adverse event varied among transfusion procedures), a separate model was performed separately for blood malignancies and thalassemic pediatric patients. All analyses were replicated for patients with both transfusion procedures.

RESULTS

In our single-center experience, 12 531 randomized blood components (n = 2662 blood malignancy and n = 9869 thalassemic patients) were transfused to 214 patients (n = 144 blood malignancy and n = 70 thalassemic patients). As shown in *Table 1*, the two populations (blood malignancy and thalassemic patients) showed different characteristics and were considered separately. Age, gender, number of transfusion, time of observation, and different blood components transfused were reported in *Table 1*. Male gender was 60% and 46% in blood malignancies and thalassemic patients, respectively. Mean age was 8.5±5.3 years in blood malignancy and 19.4±12.8 years in thalassemic patients. Median time of observation was 0.50 years (interquartile range (IQR) 0.11-0.83) in blood malignancy patients and 4.9 years (IQR 3.2-4.9) in thalassemic patients.

Adverse acute event rates for total and single transfusion are reported in *Table 2*. A total of 33/12 531 (0.3%) adverse acute events occurred. Only the adverse reactions observed during hospitalization were reported in our study. They included only mild acute reactions. In particular, 4 for EA (3 minor allergic reactions, and 1

Table 1
Characteristics of transfusion-dependent pediatric patients

	Blood malignancy patients n = 44	Thalassemic patients n = 70	p-value
Male gender n (%)	87 (60.4)	32 (45.7)	0.04
Age mean (sd)	8.5 (5.3)	19.4 (12.8)	<0.001
Number of transfusion median (IQR range)	10.5 (4-25.3)	157 (63.5-209.2)	<0.001
Period of observation, years (median (IQR range)	0.50 (0.11-0.83)	4.9 (3.2-4.9)	<0.001
Type of blood components n (%)			
Packed Red Blood Cells without Buffy Coat (EC)	88 (61.1)	59 (84.3)	<0.001
Leukodepleted Red Blood Cells (EL)	84 (58.3)	66 (94.3)	<0.001
Erithro-Apheresis (EA)	2 (1.4)	20 (28.6)	<0.001*
Erithro-Plasma-Apheresis (EPA)	65 (45.1)	66 (94.3)	<0.001
Platelet Concentrates (PC)	45 (31.3)	2 (2.9)	<0.001*
Pool Platelet from Buffy Coat (Pool-PLT)	50 (34.7)	0 (0.0)	<0.001*
Platelet Apheresis (PLT-A)	45 (31.3)	0 (0.0)	<0.001*
Plasma Fresh Frozen (FFP)	16 (11.1)	1 (1.4)	0.01*
Plasma from Erithro-Plasma-Apheresis (P-EPA)	8 (5.6)	1 (1.4)	0.28*
Plasma from Platelet-Plasma-Apheresis (P-PPA)	3 (2.1)	1 (1.4)	0.99*

*Fisher's exact test

Table 2
Distribution of adverse events by each transfusion in patients subgroups

		Total	Apheresis	Whole blood	p-value
Only blood malignancy patients	(n = 144)	15/2662 (0.56%)	1/333 (0.30%)	14/2329 (0.60%)	0.493
Only thalassemic patients	(n = 70)	18/9869 (0.18%)	3/1208 (0.25%)	15/8661 (0.17%)	0.566
Blood malignancy patients with both transfusion procedures	(n = 78)	11/2248 (0.49%)	0/330 (0.0%)	1/1918 (0.57%)	0.168
Thalassemic patients with both transfusion procedures	(n = 66)	17/9860 (0.17%)	3/1208 (0.25%)	14/8652 (0.16%)	0.497

Data are reported as number of events/number of transfusion (percentage).

episode of bronchospasm); 4 for EL (2 minor allergic reactions, 1 febrile episode, and 1 episode of vomiting); and 6 for EC (3 minor allergic reactions, 1 febrile episode, and 2 episodes of vomiting). Regarding PTL transfusion, we registered 19 adverse acute events for PC (9 minor allergic reactions, 2 febrile episodes, 1 episode of vomiting, and 7 episodes of bronchospasm). No adverse acute events for PLT-A, FFP, and plasma apheresis were reported (P = NS). No significant difference in rate of adverse acute events between blood components obtained by apheresis or whole blood was observed. Data have been confirmed by considering also patients who received both types of blood components (n = 78 blood malignancies patients and n = 66 thalassemic patients for a total n = 144 pediatric patients). The interaction term between blood products and the classification of patients was not statistically significant (p = 0.13). Then, a single logistic mixed-effect model was performed (*Table 3*). No difference was found in the distribution of adverse events between blood component collected by apheresis *vs* whole blood (*Table 3*). Odds ratio (OR) of adverse events in blood components collected by apheresis *vs* whole blood adjusted by patient classification was not statistically significant (OR [95% CI], 0.75 [0.23-2.47]). Data were confirmed for patients who received both blood components (OR [95% CI], 0.68 [0.20-2.38]).

DISCUSSION

Adverse events in transfusion medicine are largely determined by the clinical conditions and the patient state of immune reactivity, in which the choice of the transfused product can be useful in limiting subsequent adverse reactions. Whereas the blood components collected both by AF and by SI are valid in the same way, the availability of both allows us to allocate the best product to a certain type of patient, reducing adverse events in a personalized dimension. Pediatric patients are more vulnerable than adults showing a higher frequency of transfusion related side effects [7]. To our knowledge, this is

Table 3
Statistical significance of transfusion adverse events: logistic mixed-effect model

	All pediatric patients		Patients Apheresis and whole blood	
	Odds Ratio of adverse events (95% CI)	p-value	Odds Ratio of adverse events (95% CI)	p-value
Apheresis *vs* whole blood	0.75 (0.23-2.47)	0.634	0.68 (0.20-2.38)	0.551
Thalassemic *vs* blood malignancy patients	0.30 (0.04-2.10)	0.223	0.34 (0.05-2.15)	0.252

the first study investigating a putative different rate of collateral effects between apheresis and whole blood collection in pediatric patients. By results, no difference in adverse acute events occurred from blood components (RBCs, PLTs, plasma) obtained by apheresis or by whole blood in blood malignancy and thalassemic pediatric patients. Interestingly, adverse acute reactions observed (n = 33) were mild and did not cause further hospitalization. This may be related to the benefits of the increased use of leukodepleted whole blood components characterized by helpful pre-storage and bedside filters, as required by Italian legislation [17]. Since it is well known that cytokines released from residual leukocytes contaminating blood components are actively involved in a number of blood transfusion complications, most authors recommended the leukodepletion, especially for selected categories of patients, such as recipients of "long-term" transfusion regimens [23]. Leukodepleted RBCs and PLTs produced both from whole blood and apheresis reduced the risk of HLA immunization in recipients, as well as transmission of new variant Creutzfeldt-Jakob or cytomegalovirus avoiding febrile reactions [24]. The introduction of apheresis changed the final blood products with modification of storage solution and a lower volumes of residual plasma, thus producing RBCs with controlled volumes and increased Hct value [25]. In addition, apheresis provided PLTs with 4 fold lower exposure to donor antigens as compared to a single pool of PCs (with a consequent lower risk of infection, development of alloimmunity, refractoriness, and transfusion-related acute lung injury in recipients).

Consistently to our data, a recent preliminary report indicated that PLT transfusion reactions did not occur more often in recipients transfused with apheresis *vs* buffy coat platelet concentrates [25]. Although apheresis RBCs present a citrate concentration 2.5-3.0-fold higher than standard RBCs (5.72±3.01 *vs* 1.88±0.31), no adverse acute events correlated to lower plasma calcium (muscle tremor, paresthesia, cardiac arrhythmia) caused by citrate toxicity were registered [25].

CONCLUSIONS

Globally, our study data confirm a low incidence of pediatric transfusion reactions (0.33%). Regarding the RBCs, our data showed that the pre-filtered RBCs collected with the AF are absolutely superimposable to those collected from SI. Indeed, the new systems of decomposition of the whole blood allow a separation of all the components of the blood in an automatic way reducing the risk of leaving a part of plasma adhered to the red cells. Consequently the use of apheresis for red blood donors, in most CTs only concerns rare phenotypes in which it is possible to collect a double unit of red blood cells tailored on donor Hb. However hematocrit of our whole red blood sacs is around 60% while apheresis has 70% and, obviously, this must be evaluated in clinical practice as it should affect transfusion intervals. As regards platelets, apheresis have shown a greater transfusion safety and they are preferred in our Center through a massive and constant policy of increasing donations.

However, our single-center experience presents many limitations due to the heterogeneity of population examined, to the possible underestimation of symptoms, due to the inability of children to report correctly pathological signs, as well as the lack of data in the population from 0 to 8 years and the patient condition of immunosuppression. In addition, reported adverse events included only reactions occurred when patients was under medical supervision. Transfusion reactions after hospital discharge was not monitored. Despite the low reported adverse events in pediatric patients, we cannot exclude the infectious risk of non-removible blood components even with the latest methods of analysis. These considerations according with the latest directives and strategies of the PBM impose an ever lower recourse to allogeneic blood components and a greater use of alternative anesthetic, pharmacological and surgical strategies to blood transfusion. Particularly, in pediatric patients we advocate large-scale planning and application of restrictive PBMs models.

In our opinion, a randomized study involving a larger number of patients should be performed to suggest additional strategies to establish more accurate criteria to prevent adverse acute reactions in transfusion-dependent pediatric patients.

Authorship contributions

MRDP, AB, LS, AS, MV, CF performed this study. MRDP, AB, LS, SS, AS, MV, GB wrote the manuscript. CN reviewed and edited the manuscript. MRDP, AB, LS, SS, MV, AS, CS, CF, GD, MC, SP, FC, RA, GB, GFN, and CN approved the final version of the manuscript. CN is the guarantor of this work.

Conflict of interest statement

The Authors declare no conflicts of interest.

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