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Blood Transfusion Reaction In Pediatric Patients Attended At A Hematology Service Of A Teaching Hospital In The Northwestern of Paraná, Brazil.

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ABSTRACT

The aim of this research was to evaluate the adverse reactions caused by blood transfusion and its components and derivatives in pediatric patients attended at the hematology service of a public university hospital in the northwestern of Paraná, Brazil, from January 2015 to December 2017. Of the medical records of 36 patients studied, the hematological diseases presented were α-thalassaemia (2.78%); sickle cell anemia (3 0.55%); sickle cell anemia + β-thalassaemia (2.78%); β-thalassaemia intermedia (5.55%); β-thalassaemia major (2.78%); β-thalassaemia minor (8.33%); hemophilia A (41.67%); hemophilia B (2.78%); and sickle cell trait + β-thalassaemia (2.78%). About the performance of blood transfusions or use of blood components, 9 (25%) of the 36 patients performed routinely or at some time during this period, and the blood component used in all of them was the filtered and phenotyped red blood cell concentrates. The blood transfusions performed for these 9 patients were 128 in the period studied, where 3 of them had transfusion reactions and related to mild allergic reaction or moderate allergic reaction. The prevention of adverse transfusion reactions in children is required, whereas changes in technology, policy and clinical practices will improve transfusion safety in children.

Keywords: Blood transfusion, pediatrics, adverse reaction, blood products, hematology.

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INTRODUCTION

Haemovigilance is a set of surveillance procedures covering the whole transfusion chain, from the collection of blood and its components to the follow up of its recipients. The purpose of a haemovigilance system is to increase the safety, efficacy and efficiency of blood transfusion by collecting and assessing information on unexpected or undesirable effects resulting from the therapeutic use of labile blood products and to prevent their occurrence and recurrence.[1,2] Haemovigilance has been an effective tool for improving transfusion practice. Now-a-days, even in developed countries, the greatest risk to the patient lies in non-infectious complications of transfusions that account for significant morbidity and mortality.

An adverse event is an undesirable and unintended occurrence temporally associated with the administration of blood or blood component before, during or after transfusion of blood or blood component. It may be the result of an error or an incident and it may or not result in a reaction in a recipient, and have been proposed by the International Society of Blood Transfusion's working party on haemovigilance.[3] Reporting of adverse events of transfusion is a component within a haemovigilance system. The adverse events may vary from mild anaphylaxis to severe hepatitis, sepsis, and death. Therefore, the thorough investigation of cases of transfusion reaction is essential to medical practice.

ATRs include many etiologies. Two main categories exist, haemolytic transfusion reactions and non-haemolytic transfusion reactions. The second category includes febrile non-haemolytic transfusion reactions (FNHTR), allergic reactions, transfusion-related acute lung injury (TRALI), and transfusion-associated circulatory overload (TACO). [4]

In some fields, available data about pediatric patients are limited. The majority of blood product use studies have been performed using adult blood products transfused to adult patients.[5] Because the paediatric population is different, paediatric patient blood management must be established. Transfusion in paediatrics requires specific guidelines, because child physiology and pathology differ significantly as compared to adults. In patient blood management, recommendations from the 2018 Frankfurt Consensus Conference[6] were focused on RBC transfusion in adult patients while ignoring paediatric transfusion.

Adverse transfusion reactions in transfused children also vary in type and frequency, but there is a better understanding of these reactions in adults than in children. However, for the most frequent adverse transfusion reactions, the overall prevalence is higher in children than in adults, with the exception of post-transfusion red blood cell alloimmunisation, which is lower, excluding patients with haemoglobinopathies. In several studies, allergic reactions were the most frequently reported adverse transfusion reaction in pediatrics, and the platelet concentrate the most frequently implicated blood product.[4,7]

According to data from the Brazilian National Health Surveillance Agency (ANVISA), for every 1,065 transfusions, there is one transfusion reaction notification, of which 85% are mild, 12.7% moderate, and 2.2% severe.[8] These figures refer to all Brazilian hospitals that are part of the Hospital Sentinel Network, regardless of the category and age range of patients. A multicenter study involving 35 pediatric teaching hospitals in the United States showed that approximately 0.95% of patients had blood transfusion reactions; children older than 2 years were the most vulnerable in this event, and most reactions were mild.[9]

Since the pediatric population presents allergic reactions more frequently than adults, allergic transfusion reactions may often be underdiagnosed; hence, it is important to analyze them. Early diagnosis of certain adverse transfusion reactions in order to initiate the best therapy and obtain a good clinical outcome. The prevention of adverse transfusion reactions in children is required, but needs further clinical studies in pediatric.

Therefore, taking these factors into account, this paper aims to describe adverse reactions due to blood transfusion occurring in pediatric population attended in the Hematology service at a teaching University Hospital.

MATERIALS AND METHODS

This study is retrospective, cross-sectional, descriptive and analytical. Data were collected from medical records on pediatric patients attended at the Hematology service of the teaching hospital of the State University of Maringá (HURM/UEM), Paraná, Brazil, from January 2015 to December 2017. In this study, the only inclusion criterion used was to be a pediatric patient (0 to 14 years old) attended by the service. Therefore, at first the medical records of all pediatric patients treated at any period or reason to be attended by this service were analyzed, which totalized 65 medical records. However, among these, 29 lacked sufficient information to be used in the characterization of the sample, totaling a sample of 36 medical records to be used in this study. About the reasons for excluding the 29 medical records were: single consultations for reviewing the neonatal screening result for hematological diseases with little or no characterization of the patient attended; a patient who was briefly admitted to this service due to complications of hematological diseases, such as acute thoracic syndrome in patients with sickle cell anemia, but his follow-up was not done with this service; the medical record does not contain data regarding hematological disease and transfusion history; and the patient who was only treated the acute condition. In addition, medical records of patients receiving urgent or emergency blood transfusions from the HURM/UEM provided by the hematology service could not be used due to the lack of a full name registered in the system and/or medical record number of pediatric patients undergoing blood transfusion at the hospital in the being informed only by the availability of the absolute number of transfusions performed.

The data collection form used to characterize the sample contained the following data from each patient's medical record: full name, age, date of birth, gender, weight, blood type, city of origin, comorbidity, continuous use medications and doses, time of diagnosis of hematological disease, indication of transfusion, transfusions performed from 2015 to 2017 with their transfusion volumes and hemoglobin values, as well as other medications used during transfusion (e.g., antihistamines used to prevent allergic reactions), history of reaction episodes and adverse effects of transfusions, such as symptoms presented, the time between transfusion and reaction, definitive diagnosis of the reaction and the outcome.

From the collected data were analyzed by descriptive statistic using the Graph pad Prism 8.2 software. The means and standard deviations were calculated and the analysis of the categorical variables and their frequency distributions were shown.

The study was approved by Research Ethics Comitte of State University of Maringá (CAAE 08171019.4.0000.0104).

RESULTS AND DISCUSSION

The average rate of transfusion reactions reported in Paraná State, Brazil, from 2011 to 2014 was 1.5 per 1000 transfusions performed[10,11], lower than the estimate by our data (23.43 per 1000). However, for this discrepancy some factors should be considered, such as the sample size. On the other hand, the treatment of data obtained from patients with previous hematological disease and receiving repeated transfusions throughout their lives, have increased the probability to sensitization reactions to allergens present in blood products a sample considered representative of the entire population.

Of the 36 medical records selected, 26 (72.2%) patients were male, and 10 (27.8%) were female, with a mean age of 7.44 ± 3.43. Regarding the city of origin of these patients, there were 22 different cities in the northeast of Paraná State, Brazil. The hematological diseases these patients had the following diagnoses: haemophilia A, 15 (41.67%); sickle cell anemia, 11 (30.55%); β-thalassaemia minor, 3 (8.33%); β-thalassaemia intermedia, 2 (5.55%); α- thalassaemia, 1 (2.78%); sickle cell anemia + β-thalassaemia, 1 (2.78%); β-thalassaemia major, 1 (2.78%); haemophilia B, 1 (2.78%); and falcemic trace + β-thalassaemia, 1 (2.78%).

It was also raised during the analysis of medical records the age at which the diagnosis of these hematological diseases was made, whereas, 20 (55.55%) during the neonatal screening performed; 4 (11.11%) at age of one year; 3 (8.33%) at age of 3 years old; and 11 (25.01%) unknown. When the age of diagnosis of patients' hematological diseases was evaluated, it was verified a significant number of patients who had their pathology already diagnosed in neonatal screening by the newborn blood spot (heel prick) test. This test is performed for preventive actions and responsible for early identification of individuals with metabolic,

genetic, enzymatic and endocrine diseases, so that they can be treated in a timely manner, avoiding the sequel and even death. It also proposes the management of positive cases by monitoring and accompanying the child during the treatment process. In this study, only one patient showed a hemoglobinopathy potentially diagnosed late at 1 year of age as a case of β-thalassaemia by neonatal screening. All the others with Sickle Cell Disease or Thalassemia, hemoglobinopathies diagnosed by the heel prick test received this early diagnosis, showing the importance of this test for the diagnosis, treatment and early monitoring of complications of these diseases.[11] The other four patients who had their hematological disease diagnosed late, Hemophilia C was confirmed since it is a pathology not screened by this test. Our data showed that 16 (44.44%) patients were hemophilics. The diagnosis of hemophilia should be considered whenever there is a history of easy bleeding after minor trauma, or spontaneous, which may be subcutaneous hematomas in the first years of life, or muscle and/or joint bleeding in boys over two years, or even with a history of excessive bleeding after surgical procedures or tooth extraction.[12] In our study, data of blood transfusion in hemophiliac patients were not found because the protocol for their treatment include the replacement of poor coagulation factor, VIII in hemophilia A or IX in hemophilia B, and the use of other hemostatic agents.

About the patients who underwent transfusion, data indicated that there are patients with sickle cell anemia and/or β-talassaemia receiving or not transfusion, respecting specific recommendation for these pathologies. In the sickle cell disease, transfusions may be necessary to replace blood volume by bleeding or splenic sequestration or to increase oxygen carrying capacity, as in anemia exacerbations. β-thalassaemia covers three clinical presentations, according to the genetic alteration in chromosome 11: β-thalassaemia minor / β-thalassaemic trace (mild anemia), β-thalassaemia intermedia (from mild to severe anemia, which may require sporadic or chronic blood transfusions) and β-thalassaemia major (severe anemia requiring blood transfusions every 2 to 4 weeks from the first months of life).[8,12,13]

Regarding the performance of blood transfusions or the use of blood components, 9 out of 36 patients were routinely or at some time during this period, and the blood component used in all of them was the filtered and phenotyped red blood cell concentrates. For these 9 patients totaled 128 blood transfusions performed during the analyzed period. To prevent allergic reactions, 30 mg of diphenhydramine was administered to all patients before blood transfusions.

During the analysis of the medical records, the patients' mean hemoglobin level was raised when transfusion was indicated by an average of 6.18 ± 1.98g/dL. In chronic conditions with compensated anemia, such as hemoglobinopathies, hemoglobin levels of 5g / dL are well tolerated and transfusion may be indicated only when there is heart failure, dyspnea, and central nervous system dysfunction. Transfusions should be performed with phenotyped red cells (to avoid alloimmunization), and depleted leukocytes in the form of red cells or filtered.

Specific indications for transfusion in patients with sickle cell disease are: high risk for stroke, acute chest syndrome, aplastic anemia seizures, splenic sequestration, priapism, septicemia, pregnancy and before surgery.[4,6,14] These specific indications explain why some patients received transfusions with hemoglobin levels above 7g / dL, which is commonly considered the cutoff level for blood transfusion, and also justify why some patients receive an annual volume of red blood cell concentrate that is higher than others, resulting in a high standard deviation of the mean.[2,4,8]

In addition, it was verified the average volume of blood component received in each patient, given in mg / kg / year, which was 92.6 ± 127.4.mg / kg / year.

Transfusion in pediatrics requires specific guidelines, because child physiology and pathology differ significantly as compared to adults. Adverse transfusion reactions in transfused children also vary in type and frequency, but there is a better understanding of these reactions in adults than in children. However, for the most frequent adverse transfusion reactions, the overall prevalence is higher in children than in adults, except for the post-transfusion red blood cell alloimmunisation, which is lower, excluding patients with haemoglobinopathies. In several studies, allergic reactions were the most frequently reported as an adverse transfusion reaction in pediatrics, and the platelet concentrate the most frequently implicated blood product.

A multi center study involving 35 pediatric teaching hospitals in the United States showed that children older than two years were the most vulnerable to this incident and most mild type events, similar to

observed in our study.[16] About transfusion reactions, 3 were notified and were classified as "adverse reaction definitive" following the case definitions according to the NHSN BioVigilance Component Surveillance Protocol/USA.[9] Indeed, about the time of onset of symptoms, among the 3 adverse reactions presented, all were classified as "immediate" (up to 24 hours after transfusion), and two of the three presented as urticaria and were classified as "mild allergic reaction", and the other case was presented as edema and classified as "moderate allergic reaction". These denominations are in accordance with the classification suggested by the Guide for the Use of Blood Components of the Brazilian Ministry of Health.[8,14] The therapeutic conduct was similar in two of the adverse reaction cases, being hydrocortisone associated with diphenhydramine administration prescribed, presenting a rapidly favorable outcome. The third patient did not need medication, since a spontaneous resolution occurred.

Therapeutic protocol for management of a mild allergic transfusion reactions include the administration of antihistamines, e.g., diphenhydramine for symptomatic relief, as performed in two of the three reaction cases in our study. Patients with a history of allergic transfusion reactions should be closely monitored when receiving transfusions. There is no evidence to support routine antihistamine or glucocorticoid prophylaxis in patients with mild pre-transfusion allergic reactions, but antihistamine prophylaxis are commonly used in hematology services in hospital. Patients with moderate to severe allergic transfusion reactions should be advised about their diagnosis and needs for future transfusions. In these, pretreatment with antihistamines, minimization of unit plasma content removal of supernatant excess (centrifugation or rinsing), or use of platelets stored in additive solutions reduces incidence or decreases severity of adverse reactions. The use of corticosteroids as a pretreatment has not been studied, but is widely used in some services.[6,8,15]

In this work, the profile of transfusion reactions was mild events, predominantly allergic, with favorable outcomes, involving poly transfused patients, older than 2 years old, without recurrence, involving red blood cells concentrate. As the whole sample is about patients with hematological diseases, usually poly transfused and receiving red blood cells concentrates, it is not possible to evaluate which is the main variable involved in the presence of reactions, and the whole population is exposed to the same factors. Noteworthy is the lack of studies and national data surveys describing the incidence and factors related to adverse reactions in transfusions in the pediatric population, thus making comparisons difficult. In addition, the lack of a unified system that provides specific medical record data from patients in the hematology service studied who received blood or blood products for other reasons (e.g., pre-surgery and severe trauma) makes it impossible to collect data from this population, making it difficult to analyze data, since there are many factors implicated in the presence of adverse reactions.

Early diagnosis of certain adverse transfusion reactions is essential in order to initiate the best therapy and obtain a good clinical outcome. The prevention of adverse transfusion reactions in children is required, but needs further clinical studies in pediatrics. Lastly, changes in technology, policy and clinical practices will improve transfusion safety in children.

REFERENCES

[1] Faber JC. Worldwide overview of existing haemovigilance systems. *Transfus Apher Sci* 2004; *31*: 99-110.

[2] de Vries RR, Faber JC, Strengers PF. Haemovigilance: an effective tool for improving transfusion practice. *Vox Sanguinis* 2011; *100*: 60–67.

[3] ISBT working party on haemovigilance. Proposed standart definitions for surveillance of non infectious adverse transfusion reactions July 2011. Incorporating correction to Tralli definition (as adopted June 2013); 20011 http://www.isbweb.org/fileadmin/user upload/Proposed definitions 2011 surveillance non infectious adverse reactions hemovigilance incl TRALI correction 2013.pdf

[4] Moncharmont P. Adverse transfusion reaction in transfused children. *Transf Clin Biol* 2019; *in press*. doi: 10.1016/j.tracli.2019.08.002. Epub 2019 Aug 31.

[5] Goodrich RP, Sagatchian J. Special considerations for the use of pathogen reduced blood components in pediatric patients: an overview. *Transfus Apher Sci* 2018; 57:374-7.

[6] Mueller MM, Remoorttel H, Meybohm P, Aranko K, Aubron C, et al. Patient blood management recommendations from the 2018 Frankfurt concensus conference. *JAMA* 2019; 2019; 32:983-97.

[7] Pedrosa AK, Pinto FJ, Lins LD, Deus GM. Blood transfusion reactions in children: associated factors. *J Pediatria* 2013; *89*:400-6.

[8] Brasil. Ministerio da Saúde. Secretaria de Atenção à saúde. Departamento de Atenção Especializada e Temática. Caderno de Informação:sangue e hemoderivados : dados de 2015 [recurso eletrônico]/Ministério da Saúde, Secretaria de Atenção à Saúde, Departamento de Atenção Especializada e Temática.–Brasília: Ministério da Saúde, 2017. 118 p.:il. Disponível em: http://bvsms.saude.gov.br/bvs/publicacoes/caderno_informação sangue_hemoderivados_2015.pdf

[9] U.S. Centers for Disease Control and Prevention. The National Healthcare Safety Network (NHSN) Manual: Biovigilance Component Hemovigilance Module Surveillance Protocol v2.5.2. Atlanta, GA: Division of Healthcare Quality Promotion, National Center for Emerging and Zoonotic Infectious Diseases. E.U.A, 2018. Disponível em: https://www.cdc.gov/nhsn/pdfs/biovigilance/bv-hv-protocol-current.pdf.

[10] Brasil, Agência Nacional de Vigilância Sanitária. Boletim de Hemovigilância n°7. Brasília, 2015. [acessado em 12 de agosto de 2019]. Disponível em: http://portal.anvisa.gov.br/documents/33868/405222/Boletim+de+Hemovigil%C3%A2ncia+n%C2%BA+7/6e7fecae-919c-4b5b-9723-b3552ea0295f

[11] Brasil, Ministério da Saúde. Triagem neonatal biológica: Manual técnico. Brasília, 2016. [acessado em 12 de agosto de 2019]. Disponível em http://bvsms.saude.gov.br/bvs/publicacoes/triagem_neonatal_biologica_manual_tecnic . pdf

[12] Brasil, Ministério da Saúde. Manual de Hemofilia. Brasília, 2015. [acessado em 12 de novembro de 2019]. Disponível em http://bvsms.saude.gov.br/bvs/publicacoes/manual_hemofilia_2ed.pdf

[13] Brasil, Ministério da Saúde. Orientações para o diagnóstico e tratamento das Talassemias Beta. Brasília, 2016. [acessado em 12 de agosto de 2019]. Disponível em:http://bvsms.saude.gov.br/bvs/publicacoes/orientacoes_diagnostico_tratamento_talassemias_beta.pdf

[14] Brasil, Ministério da Saúde. Guia para o uso de hemocomponentes. Brasília, 2010. [acessado em 12 de novembro de 2019]. Disponível em: http://bvsms.saude.gov.br/bvs/publicacoes/guia_uso_hemocomponentes.pdf.

[15] Tinegate H, Birchall J, Gray A, Haggas R, Massey E, Norfolk D et al. Guideline on the investigation and management of acute transfusion reactions. Prepared by the BCSH Blood Transfusion Task Force. *Br J Haematol* 2012; *159*:143-53.