

Transfusion Reaction and Hemovigilance: an Imperative Discussion in Brazilian Hemotherapy Services

OPINION

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Abstract

Transfusion of blood components is considered safer, but it took years to reach this level. One of the most effective ways to make blood transfusion a safer practice is hemovigilance, which provides important data, including the history of feared transfusion reactions. In recent years in Brazil, there has been an improvement in the reporting of transfusion reactions, however due to the great diversity of hematology services, there are still transfusion reactions. The aims of this study were described the main types of transfusion reactions, as well as to evaluate the underreporting importance of transfusion occurrences of hemotherapy services in Brazil.

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Introduction

Transfusion therapy has been widely used worldwide by obtaining blood components from the total blood donated for the treatment of specific hemotherapeutic need of patients and it is a relevant clinical support [1].

As in all of the healthcare area, hemotherapy has developed and made use of procedures that aim at the well-being and safety of patients who need this important transfusion support [1-5].

The risks inherent to the transfusion practice have been increasingly discussed and measures have been taken so that they are minimized. Such fact is notable due to recent and constant updates of the legislation, such as the obligation of Nucleic Acid Tests (NAT) for HIV and HCV and the discarding of plasma components from multipara female donors due to TRALI (transfusion-related acute lung injury) risk, among other relevant updates [6].

The insertion of information related to immediate and delayed transfusion reactions in the NOTIVISA system for hemovigilance has grown in the past 13 years, since its implantation on the Sentinela network in 2002, and started being used by all hemotherapy services in Brazil in 2007. In that manner, this has helped increase the measures suitable for the improvement of hemotherapeutic processes although underreporting is a barrier to overcome [7].

This paper aims to list and compare the main immediate and delayed transfusion reactions through bulletins published by ANVISA between 2007 and 2013.

Casuistry and Method

This paper was carried out through the gathering of hemovigilance reports of transfusion reactions as well as their underreporting, published on their website, in addition to the gathering of scientific articles and pertinent bibliography.

Reactions transfusion

Even with all the technology available in hematology centers and transfusion agencies, it is still a common occurrence of transfusion events. Late reactions, transmission of viral agents, parasitic and bacterial the blood, graft-versus-host disease (GVHD), tardive haemolytic reaction, TRALI and the appearance of

irregular antibodies or alloimmunization are some examples [7]. The principal reactions are discussed next.

Immediate transfusion reactions

Immediate reactions are those occurring for or up to 24 hours after the transfusion [7].

Non-hemolytic febrile transfusion reaction

Non-Hemolytic Febrile Transfusion Reaction (NHFT) is the most commonly observed transfusion reaction. It is considered a non-specific immune reaction with the formation of the antigen-antibody complex, the activation of the complement system and the release of cytokines; antibodies of the HLA (human leukocyte antigen) and HPA (human platelet antigen) system may be present. It occurs with the increase of at least one degree in the body temperature of the recipient in up to 24 hours after the transfusion, without any other apparent cause [14, 15].

The leukodepletion of blood components before they are stored is a prophylactic measure [16-18].

Allergic/anaphylactic transfusion reaction

Normally transfusion allergic reactions (ATR) do not pose any risk to recipients; The passive transfer of antibodies and/or reagents present in the plasma of the blood component interact with reagents and/or antibodies of the recipient and result in a release of histamine by mast cells, thereby causing local erythema, pruritus and urticaria. Serious allergic reactions with IgA hypersensitivity due to lack of this immunoglobulin appear suddenly and result in the following two symptoms: cough, dyspnea, nausea, vomiting, bronchospasm, flushing, chest pain, hypotension, abdominal cramps, diarrhea, Shock and can lead to death [21, 22].

Premedication with antihistaminic drugs is used as prophylaxis. In the case of more intense allergic reactions, washing of the blood component is performed as a preventive measure [21].

Bacterial contamination reaction

Transfusion reactions related to bacterial contamination are due to the endotoxins produced by psychrophilic bacteria [21, 23].

The blood components that are often involved with bacterial contamination are packed red blood cells and platelets, but there are descriptions of cases with fresh frozen plasma and cryoprecipitate, especially during manipulation for thawing and posterior infusion [24].

The clinical signs and symptoms presented by bacterial contamination of transfused blood components are usually severe. The reaction occurs together with the presence of fever, with the increased temperature being able to reach one to two degrees above the temperature measured at the beginning of the transfusion, chills, tremors, hypotension, nausea, vomiting and shock. Other signs are flushing, dry skin, dyspnea, pains, diarrhea, hemoglobinuria, disseminated intravascular coagulation (DIC) and renal failure [21, 25-28].

The culture of the patients' blood and blood components involved in the reaction must be performed [29].

Immune acute hemolytic transfusion reaction

Immune acute hemolytic transfusion reactions occur during or immediately after the transfusion and they are secondary to the incompatibility between the donor and the recipient. They occur with the destruction of red blood cells by releasing hemoglobin into the circulation. They are characterized by the formation of the antigen-antibody complex with the activation or non-activation of the complement system. They may cause intra- or extravascular hemolysis [14, 30, 31].

The clinical signs and symptoms that characterize IHTRs are: fever, chills, flushing, chest pain, back pain, hypotension, abdominal pain, nausea, dyspnea, vomiting, hemoglobinemia, hemoglobinuria, shock, anemia, renal failure, pain at the transfusion

site, generalized hemorrhage, hives, disseminated intravascular coagulation [21, 32, 33].

Non-cardiogenic pulmonary edema/trali (transfusion-related acute lung injury)

The mechanism through which the non-cardiogenic pulmonary edema/TRALI appears is not very clear; however, it has been defined as a complication of the transfusion of blood components containing plasma, which are: total blood, packed red blood cells, packed random platelets or platelet apheresis, granulocyte apheresis, fresh frozen plasma and cryoprecipitate. In most cases, such complication occurs in the passive transfer of alloantibodies originating from donors who have been previously sensitized by leukocyte antigens [8, 34]. As an attempt to reduce TRALI risk, ordinance no. 2.712/2013 of the Ministry of Health suggests the adoption, by the hemotherapy services, of the donor assessment policy for preventing TRALI, by taking the donor's sex and the number of pregnancies of female donors into consideration [6, 35-37].

The reaction occurs together with hypoxemia and non-cardiogenic pulmonary edema, which occur from four to six hours after the transfusion and are easily confused with other clinical complications, such as volume overload in patients with congestive heart failure. In order to define the TRALI setting correctly, it is necessary to verify the pre-transfusion non-existence of acute pulmonary failure and the appearance of signs and symptoms during or within six hours before the transfusion without risk factors for such clinical condition [14]. The clinical signs and symptoms that characterize this type of reaction are: chills, cough, fever, cyanosis, hypotension and dyspnea within six hours after the transfusion [21, 35, 38, 39].

Non-immune hemolytic transfusion reaction

Non-immune hemolytic transfusion reactions are uncommon and may be related to the obtainment,

storing and preparation of the packed red blood cells. The most common causes are: Thermal lesion, osmotic lesion, mechanical lesion, bacterial contamination and clinical conditions of blood donors. When hemolysis occurs in the recipient and immunological causes are discarded, the non-immune causes listed above are suspected. The hemolysis caused by damage to the red blood cells of the donor before the transfusion results in the presence of hemoglobinemia and hemoglobinuria in the recipient, even in the absence of significant clinical symptoms. [29].

Non-immune hemolysis must be investigated, including the aspects of production and storage of infused blood components [13].

Hypotensive reaction

Hypotensive reactions occur in the absence of signs and symptoms for other reactions. The cause is not well established, but histamine is believed to be released in patients using angiotensin converting enzyme (ACE) inhibitors and using a bedding leukocyte depletion filter at the time of transfusion. During hypotensive reactions, there is a reduction of at least ten millimeters of mercury in systolic and diastolic blood pressure; This occurs in conjunction with anxiety, malaise and sweating, but fever does not occur [29, 40, 41].

Volume overload

Volume overload is the result of massive transfusions in patients with decreased cardiac reserve and is usually associated with adults over sixty years old and newborns, who can experience the reaction even with small volumes of blood components transfused. The clinical signs and symptoms are: dyspnea, cyanosis, tachycardia, edemas and increased blood pressure, which appear a few hours after the transfusion; other manifestations include headache, chest pain and dry cough. This reaction is easily confused with TRALI. Transfusions must be administered slowly, and patients must use fast-acting diuretic drugs [13, 21, 42, 43].

Delayed transfusion reactions

Delayed reactions are those occurring twenty-four hours after the transfusion [7].

Transmissible diseases

At every donation, the conduction of high-sensitive serum tests for the detection of the infectious diseases transmitted by blood, such as AIDS, Hepatitis B, Hepatitis C, Syphilis, Chagas disease, HTLV I and II and malaria, in endemic regions is mandatory, in addition to clinical screening and NAT (Nucleic Acid Tests) implantation for HIV and HCV [6, 44]. Such measures aim to avoid the transmission of diseases through the transfusion act. However, residual risk is still present. The transmission of infectious diseases by blood transfusion may be considered as a delayed transfusion reaction. The seroconversion of a donor or recipient must be investigated and reported to hemovigilance [45-48].

Transfusion-associated graft-versus-host disease - GVHD

The transfusion-associated GVHD is rare and is related to the proliferation of the T-lymphocyte originated from the blood component transfused, which responds immunologically to histocompatibility antigens; patients with cell immunodeficiency may not be able to reject transfused lymphocytes [21]. The risk of developing TA-GVHD also depends on the immunity of the patient and on the level of HLA compatibility between the donor and the recipient [29]. The clinical signs and symptoms of TA-GVHD are: fever, increased hepatic enzymes, diarrhea, rash progressing from peeling and they occur from three to thirty days after the transfusion [21]. The treatment of TA-GVHD is not effective, so the irradiation of the cell blood components is fundamental for prevention, especially in patients who are in the risk group for developing TA-GVHD [29, 49-51].

Delayed hemolytic transfusion reaction

Delayed hemolytic transfusion reactions (DHTR) occur as of twenty-four hours after the transfusion [29, 52]. It is a result of an anamnestic response in a patient who has been previously sensitized by pregnancy, transfusion or transplant and in whom the presence of baseline antibodies are not detectable in laboratory routines. They are less serious compared to IHTRs, causing mild fever or chills. Moderate jaundice may be observed [21, 53-56].

Appearance of irregular antibodies/ isoimmunization

The formation of irregular antibodies is related to the previous exposure to red blood cell antigens through the transfusion or pregnancy. The alloimmunization diagnosis is performed with the detection of a new antibody in the serum or eluate of patients recently transfused whose pre-transfusion researches were negative for anti-red blood cell antibodies. The use of packed red blood cells phenotyped for more immunogenic red blood cell antigens (RH, Kell system) may be an alternative for preventing the formation of new anti-RBC antibodies, especially for patients who are politransfused and in chronic transfusion schemes [7, 9, 57].

According to data of the hemovigilance report, the mean number of transfusions that occurred in Brazil from 2007 to 2013 was 3,341,961 (three million three hundred forty-one thousand nine hundred sixty-one) every year, so the transfusion practice is very widespread and necessary throughout the country. Therefore, the correct identification and subsequent notification of transfusion reactions is increasingly more important and fundamental for the assertive conduct for the patient and these reactions must be treated as part of the process and not as eventualities of it. The mean number of transfusion reactions reported in Brazil in the period mentioned was 5,239. This number corresponds to 0.16% of the transfusions performed; however, underreported cases are as much as 45.8% within the

abovementioned period. This means that, in addition to the percentage measured, we need to equalize underreporting, also dealing with cases that are not diagnosed, either due to the lack of verification and patient follow-up or due to the lack of training of countless professionals involved in patient care to identify the transfusion reaction correctly.

Underreporting is estimated based on three transfusion reactions for every thousand transfusions. This calculation is made based on the French hemovigilance system (*Système Français D'hémovigilance*). It is important to emphasize that, as per Anvisa data, the number of underreported cases tends to decline, either due to a greater collaboration from the hemotherapy services or to the fact that notification via NOTIVISA system became easier [7].

As in Brazil, data from The Aga Khan University Hospital Karachi in Pakistan and the Emergency Medicine, Keck School of Medicine, University of Southern California in the USA show that the transfusion reactions more commonly reported to hemovigilance are non-hemolytic febrile transfusion reactions and allergic reactions; however, there is a greater number of notifications in international services than national services. In spite of this fact, the number of notifications in Brazil has been increasing over the years [52, 58].

Regarding the transmission of infectious diseases, a reduced rate is verified compared to other transfusion reactions. Over the years, clinical and serological screenings improved and became safer. Therefore, the transmission of infectious agents is one of the lowest risks attributed to blood transfusions and blood components, as verified in table 2, where only approximately 5% of delayed transfusion reactions notified refer to seroconversion.

For many years, the culture of underreporting transfusion reactions did not allow the discussion of concrete data, but by following the example of other countries such as Canada, which, by identifying transfusion reactions secondary to bacterial contamination in 2003 (indicating 1:51,000 blood

components transfused), managed to implement control measures and, in 2005, had already obtained positive data of 1:360,000 transfusion reactions secondary to bacterial contamination [8].

With the same goal of identifying and controlling these events, Brazil has effectively managed to reduce underreporting with the implementation of NOTIVISA as shown in **Table 2**, where the num-

ber of notifications was approximately four times greater in 2013 compared to 2007, even though the country has conducted almost 900,000 less transfusions in the same period (**Table 1**). Underreporting is also noticeable when we look at the data of death due to transfusion reaction (**Table 4**). In the comparison between the data of Brazil x Unites States, it can be verified that we have

Table 1. Transfusions performed in Brazil for region from 2007 to 2013*.

Region/State	2007	2008	2009	2010	2011	2012	2013
Central West	514,663	258,516	324,729	292,740	258,213	275,724	275,559
Northeast	848,800	618,157	891,053	635,535	481,375	574,510	554,807
North	165,568	146,330	155,511	172,680	131,704	135,202	146,529
Southeast	1.622,494	1.414,696	1.538,535	1.514,687	1.395,9600	1.396,0255	1.435,557
South	850,892	743,112	706,157	722,476	712,561	773,496	736,178
Brazil	4.002,417	3.180,8111	3.615,985	3.338,118	2.979,813	3.127,957	3.148,6299

Source: Research Hemovigilance Report 2007-2013/National Agency of Sanitary Surveillance, ANVISA [7].

Table 2. Frequency of transfusion reactions notified, according to reaction type, diagnosis and year of occurrence, Brazil 2007 to 2013.

Reaction Diagnosis	2007	2008	2009	2010	2011	2012	2013
Immediate							
Non-hemolytic febrile reaction	1194	1213	1874	2470	3397	3772	3906
Allergic reaction	728	919	1420	1770	2512	3255	3219
Anaphylactic reaction	14	16	32	39	37	39	52
Bacterial infection	7	12	6	10	10	14	09
Immunological acute hemolytic reaction	15	8	26	16	35	27	23
TRALI	20	25	25	30	50	70	47
Non-immune acute hemolytic reaction	4	4	14	13	9	6	15
Hypotensive reaction	7	9	17	20	31	61	61
Volume overload	51	76	124	136	254	325	359
Other immediate reactions	137	115	218	336	447	518	346
Subtotal	2177	2397	3756	4840	6782	8087	8037
Delayed							
Transmissible diseases	3	6	2	10	8	16	4
GVHD	0	0	0	0	0	0	0
Delayed hemolytic reaction	3	1	4	7	1	5	10
Irregular alloantibodies	60	62	46	56	49	75	67
Other delayed reactions	3	11	20	15	17	19	14
Subtotal	69	80	72	88	75	115	95
Total	2253	2477	3828	4928	6857	8202	8132

Source: Hemovigilance Report 2007-2013/National Agency of Sanitary Surveillance; ANVISA [7].

Table 3. Comparison United Kingdom x Brazil x Netherlands of delayed transfusion reactions for seroconversion.

	UK (SHOT)	Brazil	Netherlands
Transfusions of 2012	2.9 million	3.1 million	-
Death Risk (estimated)	1 in 322,580	-	-
HBV transmission	1 in 1.3 million	1 report ¹ (0)	-
HCV transmission	1 in 28 million	3 reports ² (2)	-
HIV transmission	1 in 6.7 million	7 reports ³ (2)	-
Reports of 2011	-	2.9 reports per 1000 components issued	3.9 reports per 1000 components issued

¹: case reported in 2012, transfusion performed in 2011, without confirmation of transfusion origin.

²: cases reported in 2012, transfusions performed in 2010 and 2011, 2 cases confirmed.

³ cases reported in 2012, transfusions performed in 1999, 2002, 2011, 2012, 2 cases confirmed, 1 case under ongoing investigation.

Source: Maggs P.H.B, Cohen H., 2013 and Hemovigilance Report 2007-2013/National Agency of Sanitary Surveillance, ANVISA [7, 8].

Table 3. Comparison of death cases reported in the United States x Brazil.

	USA (FDA – Food and Drug Administration)	Brazil
	2008 - 2012	2007-2013
TRALI	74	-
Hemolytic transfusion reaction (non-ABO)	31	-
Hemolytic transfusion reactions (ABO)	22	-
Microbial infection	21	-
TACO	35	-
Anaphylaxis	12	-
Other	3	-
Total	198	55 *

*: The death cases have not been classified per transfusion reaction type in Brazil.

Source: Bolton-Maggs P.H.B, Cohen H., 2013 and hemovigilance report, 2013[7, 8].

considerably lower absolute numbers in the longer analysis period and, in addition, Brazil has not established deaths by reaction type, which weakens the information and makes taking action more difficult.

Brazil is still in an increasing curve in the absolute number of transfusion reaction notifications, (**Table 2**) which apparently only shows a decline in the number of underreported cases and cannot confirm an effective increase of transfusion reactions due to the recent improvement and education of hemotherapeutic services in this evolution line.

The identification of transfusion reactions by the healthcare team is a great challenge, considering the similarity among events, with similar signs and symptoms, thus generating questions of general and inaccurate diagnoses [59, 60].

The work of the professionals on the awareness of the importance of notification and correct diagnosis is fundamental for the patient because it implies an effective medical conduct for the next transfusions and notification becomes the most realistic system and guides hemovigilance to assertive mechanisms with work fronts, enabling data in accordance with the reality and providing preventive measures.

Discussion

Hemovigilance is defined as the collection of information on transfusion complications, data analysis and subsequent improvement in transfusion practice. The main goal in developing hemovigilance programs is to increase the number of notifications of transfusion adverse events [9-12].

The correct diagnosis and therapeutic conduct regarding transfusion reactions is almost as important as the transfusion act itself, thus making the use of blood components safer and more effective in the treatment for which it is used [13].

The hemovigilance system in Brazil was developed as of 2002 and its implantation was initiated as a pilot project in a hospital network called Sentinela,

which notified adverse events and technical complaints related to health products in the Notification Information System. With the implantation of the Notification System in Health Surveillance (Notivisa) via web in December 2006, the possibility to notify transfusion reactions to all health services performing blood transfusions was increased [7].

According to the hemovigilance notification form of the National Health Surveillance Agency – ANVISA, transfusion reactions can be classified as immediate or delayed transfusion reactions.

The following are listed among immediate reactions: non-hemolytic febrile reaction (NHFR), allergic reaction, anaphylactic reaction, bacterial infection reaction, immune acute hemolytic reaction, non-cardiogenic pulmonary edema/TRALI (transfusion-related acute lung injury), non-immune acute hemolytic reaction, hypotensive reaction and volume overload.

The following are listed among delayed reactions: transmissible diseases, graft-versus-host disease (GVHD), delayed hemolytic reaction and the appearance of irregular antibodies/isoimmunization [7].

Conclusion

Transfusion is a widely used therapeutic measure and, as in any medical procedure, there are risks inherent to the process. Transfusion reactions happen in approximately 2.6% of the transfusions performed in Brazil.

Hemovigilance, whose main function is taking actions that widen and improve safety in blood transfusions, with special emphasis in transfusion incidents, has improved and been through positive changes within the last 13 years. Moreover, in the last 7 years, it has counted on the help of all hemotherapeutic assistance to the patient in order to consolidate the NOTIVISA system. The implantation of the system of transfusion reaction notification has led to a greater control of the incidences, but there is still a long way to go.

The similarity of signs and symptoms and the lack of training and assistance to the patient for the identification of transfusion reactions is an obstacle to be overcome.

The educative measures to raise the awareness of the hemotherapeutic services must be increasingly widespread and effective control measures on non-reported notifications must be taken with actions aimed at the small number of notifications by hemotherapeutic services.

Declarations of Interests

The authors declare there are no conflicts of interest.

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