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Research Article

NEGLECTED TROPICAL DISEASES TRANSMITTED BY BLOOD TRANSFUSION: CURRENT OVERVIEW IN BRAZIL

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A B S T R A C T

This article aims to demonstrate the current hemotherapy situation of the main neglected diseases with potential for transmission by blood transfusion. The focus of this review is to show the possible difficulties faced by blood banks in the screening process for each disease cited. Throughout the article, the authors report that the main problems faced by blood banks correspond to the poor performance of serological tests, absence of gold standard techniques, lack of effective regulatory policies in the area of hemotherapy and ineffective hemovigilance actions. Given the above, it is concluded that pathogen inactivation techniques can alleviate such problems and thus increase the transfusional safety in Brazil and worldwide.

INTRODUCTION

Neglected tropical diseases are a group of endemic infectious-contagious diseases, which refer to a diverse group of diseases that are closely linked to poverty and the inefficiency of control policies. They occur mainly in tropical and subtropical countries, affecting marginalized communities in poor rural and urban environments, especially in underdeveloped countries in Africa, Asia and Latin America. Together, these diseases can cause more than one (1) million deaths annually (WHO, 2019). In this manuscript, we will address the general panorama of Chagas Disease, Malaria, Visceral Leishmaniasis and arboviruses (Dengue, Zika and Chikungunya) - diseases that have wide distribution worldwide and that have as a common characteristic the bite of an insect vector as the main form of transmission, but they have well-documented reports in the scientific literature of cases of transfusional transmission.

The possibility of transmission of infectious diseases by blood transfusion has been recognized for over a century, with the publication of the first case of transfusional malaria in 1911 (Woolsey, 1911). It is now known that any infection by an agent that goes through an asymptomatic blood phase has the potential to be inadvertently transmitted by transfusion. Other necessary characteristics include the ability of the infectious agent to survive the processing and preservation of blood products and the ability to cause significant disease when transmitted by the blood. Factors dependent not only on the infectious agent but also on the recipient, such as their immune status, will determine the frequency and severity of transmitted infections (Ferreira-Silva, *et al*, 2020).

Regarding Chagas disease, among the four diseases mentioned in this article, it is the only one that has well-defined screening processes in blood banks in Brazil, including those regulated by the appropriate Brazilian health agencies and with wide serological coverage (ANVISA, 2016). Despite the high sensitivity of anti-*Trypanosoma cruzi* serological tests and, at the same time, the low prevalence of chagasic donors, the wide variation in the specificity indices of serological tests is noteworthy, generating significant indices of inconclusion and/or serological discrepancy between donors, which they can reach almost 70% (Furuchó, 2008; Ferreira-Silva *et al*, 2020). Studies show that inconclusive reactions may be superior to positive reactions in serologic disabilities for Chagas disease (Ferreira-Silva, *et al* 2020). Therefore, currently the main focus of research related to DChT has been on state-of-the-art diagnostic tests that, in addition to high sensitivity, have a specificity of practically 100%, which would avoid the

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unnecessary disposal of blood bags and also donors wrongly classified as inept.

As for malaria, there are reports of prevalence among blood donors, as well as transmission of the disease by transfusion in the five continents, with the highest number of cases in Africa, Asia and South America, being the infectious disease with the highest number of cases of transfusional transmission reported in the literature (Ferreira-Silva, *et al*, 2021). Factors such as the high prevalence rate of asymptomatic malaria carriers, as well as poor regulation of blood donor screening and an ineffective hemovigilance policy worsen the risk of Transfusional Transmissible Malaria (TTM). In endemic countries, the incidence is estimated to exceed 50 cases per million transfusions. Patients with underlying diseases or immunosuppressed that require polytransfusions are the most susceptible to TTM. After an eventual transfusion of bags contaminated by Plasmodium sp, these patients can develop the most severe form of the disease, presenting high-risk clinical complications that can culminate in a fatal outcome. According to Brazilian regulations, in endemic areas with an epidemiological history of malaria, the candidate will be considered unsuitable when who has had malaria in the 12 (twelve) months prior to the donation or with fever or suspected malaria in the last 30 (thirty) days and who have moved or come from a high-risk area (IPA greater than 49.9) for less than 30 (thirty) days. In non-endemic areas for malaria, the candidate who has moved or comes from municipalities located in endemic areas for less than 30 days will be considered unsuitable (ANVISA, 2016).

Despite these regulations, there has been no effective disease control policy in blood banks in endemic countries. There are several alternative strategies already tried or recommended in different parts of the world for the prevention of transfusional malaria. Among them, the universal prophylaxis of receptors and the adoption of pathogen reduction techniques with irradiation capable of killing plasmodium stand out. Such methodology has also been proposed for other infectious diseases such as Dengue and Visceral Leishamniosis.

Regarding arboviruses, these are viral diseases transmitted mainly by arthropods and comprise Zika, Dengue and Chikungunya, and transmission can occur in a vector or non-vector way. The vector form usually occurs during the meal of infected mosquitoes of the genus *Aedes aegypti*. The non-vector form is due to virus transmission through blood transfusions, organ transplants, among others (Gebre *et al*, 2016). The first cases of transfusional transmission of arboviruses described in the literature were dengue virus (DENV), which were documented in three blood recipients in Hong Kong in 2002 (Chuang *et al*, 2008). Since then, blood transfusion-transmitted dengue virus infections have been confirmed in different geographic locations, mainly in tropical regions, including South and Central America, as well as South and Southeast Asia, such as Brazil, Puerto Rico, Pakistan, Hong Kong and Singapore (Slavov *et al*., 2019).

Brazil is currently one of the countries with the highest number of dengue cases in the world, with the estimated risk for transfusional dengue transmission (TT DENV) being approximately 6 for every 10,000 blood transfusions. Regarding hemotherapy, the great concern is the high percentage of asymptomatic dengue virus carriers, which can range from 50% to more than 70% of cases (Sabino *et al*, 2012; Levi, *et al*, 2016; Li *et al*. 2021).

Despite these numbers, there are still no specific control measures for TT DENV. A study carried out in two Brazilian capitals showed that up to 2% of donors were infected with the virus in a typical summer period, when there is a higher incidence of the disease. This study reports that blood bags contaminated with dengue virus subtype 4 (DENV-4) were transfused into 22 recipients, six of which were effectively infected, resulting in a transfusional transmission rate of 37.5% for dengue (Sabino *et al*, 2016). Due to the high prevalence reported in the literature, serological screening for dengue virus in blood banks has been advocated by many experts, however it is known that universal screening would significantly compromise the blood supply in blood centers worldwide, leading to the system from hemotherapy to possible collapse. Thus, control policies must be created aiming at the effective control of transfusion transmission without compromising the stock of blood components. Methods of inactivating pathogens for the dengue virus have already shown effective results and are being evaluated.

As for other arboviruses, it is known that ZIKAV infections have an incubation period of three to twelve days, remaining asymptomatic in approximately 80% of infected individuals. Added to these characteristics, the rapid spread of Zika virus epidemics has made the transfusional transmission of Zika virus (TT-ZIKAV) an emerging threat to blood banks worldwide. The possibility and risk of ZIKAV transfusional transmission was first described during the French Polynesian epidemic, when asymptomatic donors had a prevalence of 2.8% (42/1,505) (Musso *et al*, 2014, Liu *et al*., 2019). In subsequent surveys, the prevalence of ZIKAV among blood donors ranged from 0.001% to 0.004% in the United States, 0.5% in Puerto Rico, and 1.84% (76/4,129) in the Caribbean region on the island of Martinique. In Brazil, the first report described was in 2016 in the State of São Paulo, in the region of Ribeirão Preto, identifying a prevalence of 2.7% in blood donors. Nevertheless, to date, only two cases of TT-ZIKAV have been described in the literature - both reported in Brazil and occurred after transfusion of platelet concentrates. (Lira *et al*., 2021).

The concern with the safety of ZIKAV-free blood and the lessons learned from previous epidemics related to other arboviruses demanded early interventions from regulatory bodies in several countries during the outbreaks and spread of the virus around the world. Based on hemovigilance policies, the measures and instruments available to certify transfusion safety include criteria for selection, clinical and epidemiological screening of candidates for donation, obtaining post-donation information, maintenance of blood components in quarantine for a period of seven days before release for transfusion; use of pathogen inactivation technologies, usually using photochemical treatment with amotosalen and ultraviolet A (UVA) light (Drew *et al*, 2017), and molecular testing of ZIKAV (NAT – Nucleic Acid Test) in blood donors (ANVISA, 2020; Lira *et al*., 2021). In Brazil, the National Health Surveillance Agency (ANVISA) and the Ministry of Health recommend that candidates for donation clinically or laboratory-diagnosed by ZIKAV should be considered unfit for donation for 120 days. In September 2015,

ANVISA approved the use of photochemical treatment for pathogen inactivation, despite this, there are no commercial ZIKAV RNA screening tests approved in Brazil (ANVISA, 2020).

As for Chikungunya, a study carried out in the north and southeast of Brazil demonstrated the importance of research, since the serum prevalence of CHIKV and the risk of transfusion in Brazil are completely unknown and outbreaks have been reported in different geographic regions of the country. The serological study carried out in the period between 2015-2016 was considered the largest to date to evaluate the prevalence of CHIKV in blood donors. A large proportion of negative results were observed in both regions included, and was associated with the slow expansion of the virus in Brazil, indicating that research of greater magnitude and involving other states should be carried out, since the dissemination is ongoing and serological surveys that can assess the epidemiological profile of the virus in blood donors are of great importance (Slavov *et al*, 2018).

The high prevalence of viraemic individuals in periods of outbreak, the frequency of transfusions and the absence of cases of the disease transmitted by transfusion, demonstrating the need for extensive measures to prevent the transfusional transmission of the virus are necessary. The lack of notification of CHIKV can include several factors such as: difficulty in differentiating transfusion transmission and mosquito transmission in large outbreak sites, insufficient hemovigilance, the existence of collective immunity to the virus in affected areas and the lack of implementation of measures such as screening for screening viral RNA in donors (Appassakij *et al*, 2019).

In the case of visceral leishmaniasis, the transmission of Leishmania sp by transfusion of blood components has been a major concern in endemic areas. There are reports of a high prevalence of seropositivity among donors from endemic and non-endemic regions. Although the vast majority of carriers are asymptomatic and have no clinical evidence of the disease, the parasite can become active and multiply in the mononuclear phagocytic system in response to factors such as the patient's immune and nutritional status and the donor's parasite load. If amastigotes survive the processing and storage of blood until the moment of transfusion, the chance of transfusional transmission of VL is high, especially in polytransfused or immunocompromised patients. In addition to the information on the feasibility of Leishmania and the usual transfusion conditions, there are case reports in the literature, in which blood transfusion has been indicated as the only explanation for contamination by visceral leishmaniasis (VL). The first cases were described in China in 1948. Later, transfusional transmission of leishmaniasis was considered probable in several articles, reporting cases that occurred even in patients from non-endemic countries such as Belgium, Germany and England, with very adverse clinical manifestations. A study by Ferreira-Silva *et al*, 2018, carried out in three endemic areas of Brazil reported a prevalence rate among blood donors of 7.2% of seropositivity for visceral leishmaniasis. Of the total grants from positive donors, six were transfused. In samples collected 30 to 60 days after transfusion of these bags, two (2) patients showed serological change to VL, indicating probable contamination by transfusion of blood components (Ferreira-Silva, *et AL* 2018). Although there are many documented cases of VL transfusion transmission, there is no commercial test available that has demonstrated high reproducibility rates for asymptomatic cases of Leishmania sp. Thus, the absence of an affordable gold standard test can make it difficult to implement an adequate serological screening in blood banks worldwide, increasing the exposure of patients to the risk of disease contamination.

CONCLUSION

Despite increased surveillance in hemotherapy services since the 1980s, several diseases that are not routinely screened for in blood banks have been recognized as presenting a potential risk of transfusion transmission. Factors such as failure in the performance of screening tests or the absence of highly reproducible commercial tests and ineffective blood regulation policies are factors that perpetuate the risk of transmission of infectious diseases through blood transfusion. Added to these factors, there is also the high prevalence of asymptomatic blood donors - but with a high probability of infectiousness for the diseases mentioned here - and the risk that the infection will manifest itself severely in recipients already weakened by underlying diseases, are concerns constant among professionals and researchers in the area of hemotherapy. Aiming to increase transfusional safety, while there are no tests in blood banks that can be considered the gold standard, research on inactivation techniques for various pathogens by leucodepletion filters or by irradiation of blood bags has been carried out in several countries and should be deepened for possible implementation in blood banks. The potential benefits already demonstrated in previous studies should be encouraging to accelerate ongoing research into techniques for pathogen inactivation and possible risk reduction from whole blood products shortly.

References

1. ANVISA 2016. RDC 102-2016. Ministério da Saúde, Brazil. Avaiable in: https://www.in.gov.br/materia//asset_publisher/Kujrw0TZC2Mb/content/id/23517143/do1-2016-08-25-resolucao-rdc-n-102-de-24-de-agosto-de-2016 Brasil. Agência Nacional de Vigilância Sanitária. Nota Técnica Nº 5/2020-CGSH/DAET/SAES/MS.
2. Brasil. Agência Nacional de Vigilância Sanitária. Nota Técnica Nº 5/2020-CGSH/DAET/SAES/MS.
3. Chuang V, Wong TY, Leung YH, Ma E, Law YL, Tsang O, Chan KM, Tsang I, Que TL, Yung R, Liu SH. Review of dengue cases in Hong Kong from 1998 to 2005. Hong Kong Med J. 2008 Jun; 14 (3): 170-7.
4. Drew VJ, Barro L, Seghatchian J, Burnouf T. Towards the inactivation of red blood cell and whole blood pathogens targeting viral DNA / RNA: design, technologies and future perspectives for developing countries. *Blood Transfus* . 2017; 15 (6): 512-521. doi: 10.2450 / 2017.0344-16.
5. Ferreira-Silva, MM, Teixeira LA, Tibúrcio MS, Pereira GA, *et al*. Socio-epidemiological characterisation of blood donors with asymptomatic Leishmania infantum infection from three Brazilian endemic regions and analysis of the transfusional transmission risk of visceral leishmaniasis.

Transfusion Medicine (Online), v. 28, p. 433-439, 2018.

6. Ferreira-Silva,MM; Pereira, GA, Rodrigues-Júnior V, Meira WSF, Moraes-Souza H, *et al*. Chagas Disease: Performance analysis of immunodiagnostic tests anti-Trypanosoma cruzi in blood donors with inconclusive screening results. Hematology, Transfusion and Cell Therapy, 2020. https://doi.org/10.1016/j.htct.2020.06.016.
7. Ferreira-Silva MM, Carlos AM, Domingos Resende GA. Malaria Transfusional Transmission: Epidemiological Review, Screening Protocols and Prevention Mechanisms. J Biomed Res Environ Sci. 2021 July 28; 2(7): 624-631. doi: 10.37871/ jbres1288, Article ID: JBRES1288, Available at: https://www.jelsciences.com/articles/jbres1288.pdf
8. Furuchó R, Umezawa ES, Almeida, L, Shikanai-Yassuda M. Inconclusive results in conventional serological screening for Chagas disease in blood banks: assessment of cellular and humoral response. Trop. Med. Intern. Health., 13 (2008), pp. 1527-1533.
9. Gebre Y, Forbes N, Gebre T. Zika vírus infection, transmission, associated neurological disorders and birth abnormalities: A review of progress in research, priorities andknowledge gaps, Asian Pacific Journal of Tropical Biomedicine, Volume 6, Issue 10, 2016, Pages 815-824. https://doi.org/10.1016/j.apjtb.2016.08.008.
10. Levi JE. Dengue vírus and Blood Transfusion. *The Journal of Infectious Diseases* , Volume 213, Issue 5, 1 de março de 2016, Pages 689-690, https://doi.org/10.1093/infdis/jiv322
11. Li L, Li Y, Lu S, Dong J, Xu H, Zhang Q, Weng R, Yin Y, He R, Fang P, Shi H, Yu Y, Wu J, Liu Z, Hess JR. Epidemiological research and screening strategy for the dengue virus in blood donors in Yunnan Province. BMC Infect Dis., 2021; 21 (1): 104. doi: 10.1186 / s12879-021-05810-8. PMID: 33482756; PMCID: PMC7821518.
12. Lira S Costa M; Levi, J E, *et al*. .Zika virus RNA detection in blood donors in São Paulo, Brazil. Hematology, Transfusion and Cell Therapy.2021; 1-6.https://doi.org/10.1016/j.htct.2021.03.007.
13. Liu, R., Wang, X., Ma, Y. *et al.* Prevalence of Zika virus in blood donations: a systematic reviewand meta-analysis. *BMC Infect Dis* **19,** 590 (2019). https://doi.org/10.1186/s12879-019-4226-6.
14. Musso, D. *et al*. Potential for Zika vírus transmission through blood transfusion demonstrated during anoutbreak in French Polynesia, November2013 to February 2014. EuroSuveill. 2014;19(14):6-8.
15. Sabino EC, Loureiro P, Lopes ME, Capuani L, Mc Clure C, Chowdhury D, Di-Lorenzo-Oliveira C, *et al*. Transfusion-transmitted dengue and associated clinical symptoms during the 2012 epidemic in Brazil. Internacional Component of NHLBI. Recipient Epidemiology and Donor Evaluation Study-III.J Infect Dis. 1 de março de 2016; 213 (5): 694-702.
16. Slovov SN, Ota, *Otaguiri KK, Bianquini ML, BitencourtHTOc, Chagas MCM, Guerreiro DSS* Seroprevalence of Chikungunya virus in blood donors from Northern and Southeastern Brazil. Hematol transfus. Cell ther., 40(4):358–362, 2018.
17. WHO. World Malaria Report 2019. World Health Organization: Geneva; 2019. Disponível em: https://www.who.int/publications/i/item/9789241565721.
18. Woolsey G. Transfusion for perniciosa anemia. Trans NY Surg Soci. 1911; 132–3.

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