Acta Tropica 115 (2010) 28–34

Contents lists available at ScienceDirect

Acta Tropica

journal homepage: www.elsevier.com/locate/actatropica

Transfusion transmitted Chagas disease: Is it really under control?

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ARTICLE INFO

Article history:
Available online 4 January 2010

Keywords:
Protozoa
American trypanosomiasis
Chagas disease
Blood transfusion
Pathogen reduction
Transfusional risk
Leukofiltration

ABSTRACT

Transfusion transmitted Chagas disease was recognized as a medical problem more than 50 years ago. However, little attention was paid to it by Transfusion Medicine, medical authorities or regulatory agencies as a major problem and threat (especially after the advent of HIV/AIDS); perhaps because it was mainly restricted to tropical regions, usually in less developed countries. With the intense human migratory movement from developing to developed countries, it became more common and evident. The scope of this review is to cover the main transfusional aspects of American trypanosomiasis (Chagas disease), including the main strategies to prevent it through donor questionnaires, specific serological testing and alternative methods such as leukofiltration and pathogen reduction procedures, in order to increase the blood safety in both developing and developed countries.

1. Introduction

Transfusion transmitted Chagas disease (TxCD) has been constantly considered as a problem in Transfusion Medicine, although its severity was deemed as variable according to different geographical regions. However, infectious diseases throughout history have always shifted from a secondary rank after appropriate Public Health measures were taken, to an emerging (or "reemerging") position, because they were regarded as a secondary problem and neglected by competent authorities. Thus, in the early 1980s, when AIDS became the main infectious disease to be controlled in Transfusion Medicine, followed by other viral diseases, particularly Hepatitis C and B viruses (HCV, HBV), and more recently West Nile Virus (WNV), a relative minor importance was given to this agent in the context of transfusion transmission and control. Table 1 depicts the main aspects related to TxCD.

Vectorial transmission of Chagas disease only occurs in the American continent, through inoculation of *Trypanosoma cruzi* after a blood meal by a reduvid bug. Transmission by blood transfusion was first suggested by Mazza in Argentina, in 1936 (Mazza et al., 1936), later supported in Brazil, Uruguay and Argentina. The first two cases of Tx Chagas disease were published in 1952 (Freitas et al., 1952) and at the same time, the value of chemoprophylaxis with crystal violet (gentian violet) was studied (Nussenzweig et al., 1953). Though regarded as a strictly Latin American problem, Chagas disease transmission through blood components became recognized in North America in the late 1980s (Geiseler et al., 1987; Grant et al., 1989; Nickerson et al., 1989; Cimo et al., 1993; Kirchhoff et al., 2006; Young et al., 2007) and subsequently in Europe, particularly in Spain (Villalba et al., 1992; Flores-Chávez et al., 2008; Piron et al., 2008; Castro, 2009).

The Southern Cone (Dias, 2007; Panamerican Health Organization, 1992) and the Andean (Panamerican Health Organization, 2003) Countries Initiatives have as their main objective, to eliminate the domiciliary infestation by *Triatoma infestans* and complete control over transfusional transmission with rigid governmental control (Panamerican Health Organization, 1997) and mandatory serological screening (Dias et al., 2002; Moncayo, 2003). This action was supported by the 51st World Health Assembly, which deemed Chagas disease control as one of its main priorities (World Health Assembly, 1998).

Since the American Continent comprises more than 20 different countries, there is a wide array of infected donors in different regions, ranging from as low as 0.01% in the USA to 60% in certain Bolivian cities (Wendel et al., 1992; Leiby et al., 1997; Wendel and Gonzaga, 1993; Wendel, 1997; Barea et al., 2004; Araújo et al., 2008; Steele et al., 2007). Nevertheless, in the past 20 years, there has been a progressive decrease in the prevalence of *T. cruzi* among blood donors from Latin American countries (Zicker et al., 1990; Massad, 2008).

With the exception of blood derivatives, all blood components are infective. *T. cruzi* remains viable at 4 °C for at least 18 days (Wendel et al., 1992) or up to 250 days when kept at room temperature. Although frozen strains are viable in cryopreserved vials, there are no clear evidences of transmission through frozen-thawed labile cellular components. Despite its theoretical possibility and the fact that hemophiliacs treated only with cryoprecipitate have been described (Schlemper, 1978; Cerisola et al., 1972), the possi-

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doi:10.1016/j.actatropica.2009.12.006

Table 1
Main features related to TxCD (Wendel, 2003).

Millions of people are infected (some blood donors), with a major economical impact (Wendel and Leiby, 2007)
Predominance in certain geographical regions (usually poor or developing tropical countries) (World Health Organization, 2002)
Chronic asymptomatic carrier present (Umezawa et al., 2001; Prata, 2001)
A vector is present (Moncayo and Ortiz Yanine, 2006)
Considered as a zoonosis, which makes eradication in the world virtually impossible (Silveira, 2002)
Transfusion cases widely undetected and unreported
Despite available treatment (mainly in acute cases), fatalities are described (Coura, 2007)
Serological screening tests available, but sensitivity and specificity are still far from ideal (Otani et al., 2009)
Gold standard not always available (imperfect gold standards) (Zhou et al., 2002)
Unlike viral diseases, *T. cruzi* is present in relatively low amounts in the bloodstream in asymptomatic cases (blood donors), requiring large volumes of blood for effective molecular screening methods (Castro et al., 2002).
Universal blood donor questionnaires have a limited value (O'Brien et al., 2008)
Sensitive to pathogen reduction methods (Webert et al., 2008)
Other ways of transmission (organ transplants, congenitally, oral intake, laboratory accidents, etc.) described, apart from vectorial and transfusional (Chocair et al., 1981; Ferraz and Figueiredo, 1993; CDC, 2006; Kun et al., 2009)
Intense immigration from affected areas to developed regions, where disease is usually absent, with low public perception of the problem (Schmunis, 2007).
Control strategies depend on political will and commitment, sometimes different for each country (Dias, 2007).

bility of vectorial transmission cannot be ruled out in some of these cases. Thus, there are unanswered questions concerning infectivity from frozen cellular products.

In many locations, blood transfusion is recognized as the second most important way for the transmission of Chagas disease; on the other hand it can be recognized as the main important route in industrialized countries (e.g. Canada, USA and Spain) (Geiseler et al., 1987; Grant et al., 1989; Nickerson et al., 1989; Cimo et al., 1993; Villalba et al., 1992; Flores-Chávez et al., 2008; Piron et al., 2008).

The true number of reported cases is also underestimated, since no more than 350 cases have been published (Wendel and Leiby, 2007; Wendel, 2003; Flores-Chávez et al., 2008; Wendel et al., 1992; De Paula et al., 2008). Although the reported cases in countries in the Northern hemisphere are quite low, there is intense Latin American emigration to these countries, with estimates of 12,400,000 immigrants to the USA, where one calculates that 89,000 to 680,000 immigrants in North America are infected by *T. cruzi* (Schmunis, 2007), and nearly 75,000 of them might show some cardiac manifestation (Milei et al., 1992). The figures in Europe are changing quite rapidly, particularly in Spain, where the National Statistic Institute of Spain (INE – www.ine.es) estimates a total of 1.8 million Latin American immigrants in this country in January 2009 (INE, 2009).

The possibility of infection from blood components depends on several factors (amount of transfused blood, parasite strain, presence of parasitaemia at the time of donation, recipient immune status and screening tests) (Wendel et al., 1992; Wendel and Gonzaga, 1993; Schmunis and Cruz, 2005). Data from the 1960s and 1970s demonstrated that the real infectivity rate derived from one infected whole blood unit is around 12–25% (Cerisola et al., 1972; Coura et al., 1966; Rohwedder, 1969), though a higher value (46.7%) was observed in Bolivia (Zuna et al., 1979). Maybe the low parasitaemia (less than 1 per 20 ml of whole blood) and the concomitant presence of antibodies in donor's bloodstream are partially responsible for incomplete infectivity. Although data is scarce regarding different patterns of infectivity as far as different components are concerned, and the fact that whole blood, and packed red cells were the main blood components associated with transmission until the 1980s in Latin America (where Blood Transfusion Services were still not quite well organized), and that recent publications clearly show that platelets are currently the most implicated components related to blood transmission, particularly in oncological patients (usually immunosuppressed) (Young et al., 2007; Fragata Filho et al., 2008), it is likely that this shift results only from the ability of parasites to survive in fresher units. Since platelets were rarely used in the past (now a common practice in the support of oncological patients in developed regions), and the main available components in Latin America in that period were whole blood (usually stored for only 21 days), there might be no reason to blame a given cellular component provided the storage period is adjusted. Nevertheless, the time-trend infectious rate from blood components still need to be determined by carefully controlled studies.

Although sensitivity of tests is lower than viral screening tests (97–99%) (Otani et al., 2009; Luquetti, 2000), universal screening has dramatically changed the associated transfusional risks in Latin America in recent years. In countries where this strategy has been fully implemented, the residual risk of infection is calculated to be around 1:200,000 units (Schmunis and Cruz, 2005; Wendel, 2005), with clustered spatial geographical distribution.

A recent Brazilian survey (Wendel et al., 2005a) comprising over 1.5 million whole blood donations, demonstrated that the estimated prevalence of *T. cruzi* infected donors has a crescent age-related positivity. Interpolation by ordinary anisotropic point kriging analysis resulted in risk areas in the country both for false positive and negative data in four different regions (where vectorial activity is still found) and the presence of a possible new risk area in the Amazon region, with national estimates of false negative results of 0.9–7.4 cases per 100,000 whole blood donations, rendering some 0.44–2.75:100,000 infectious blood components to recipients. This survey concluded that the residual *T. cruzi* risk transmitted by blood transfusion in Brazil is 10–15-fold as compared to HIV, HBV or HCV, with a spatial concentration in the country. Data from other Latin American countries, using different estimate approaches are also described (Wendel et al., 1992; Schmunis and Cruz, 2005).

The incubation period of acute Chagas disease following an infected blood unit varies from 20 to 40 days (range: 8–120 days). Fever is the most common and sometimes the only manifestation (Bergoglio, 1965). In the most severe cases (lymphadenopathy, hepatosplenomegaly, cardiac arrhythmia) central nervous system involvement may be present and the association of these latter symptoms must always be suspected as Chagas disease in recipients transfused from untested donors (Bergoglio, 1984).

Approximately 20% of infected recipients are completely asymptomatic, raising no suspicion of diagnosis (Wendel et al., 1992). In fact, in non-endemic areas in industrialized countries, this rate might be somewhat higher than in endemic countries (Kerleguer et al., 2007; Comeau, 2007; Garraud et al., 2007; Leiby et al., 2008), due to lack of medical expertise and awareness.

A spontaneous recovery will ensue 6–8 weeks after the acute phase, but may extend for up to 4 months. Thereafter, the disease follows its natural course to an indeterminate phase (persisting for years or decades), representing the majority of cases. In the chronic phase, cardiac, gastrointestinal or neurological symptoms are observed after several years, usually not linked to an acute phase. More comprehensive data about the chronic manifestations of Chagas disease can be found elsewhere (Umezawa et al., 2001; Prata, 2001; Flores-Chávez et al., 2008; Wendel et al., 1992).

Prevention of Tx Chagas disease can be accomplished by three different strategies: (a) *Anamnesis and questionnaires to the donors* — there is a trend to find more infected donors among those with higher age, first time or replacement donation, or the period of living in endemic areas (Zicker et al., 1990; Wendel, 2005; Wendel and Biagini, 1995; Sabino et al., 2003). In endemic and non-endemic regions, donors who lived in infested dwellings or acknowledged