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EVALUATION OF SURROGATE MARKERS FOR HUMAN IMMUNODEFICIENCY VIRUS INFECTION AMONG BLOOD DONORS AT THE BLOOD BANK OF "HOSPITAL UNIVERSITÁRIO REGIONAL NORTE DO PARANÁ", LONDRINA, PR, BRAZIL

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SUMMARY

This study evaluated the usefulness of the anti-HBc, hepatitis C virus antibodies (anti-HCV), human T cell lymphotropic virus I and II antibodies (anti-HTLV I/II), serologic tests for syphilis, and surface antigen of hepatitis B virus (HBsAg) as surrogate markers for the risk for HIV infection in 80,284 serum samples from blood donors from the Blood Bank of "Hospital Universitário Regional Norte do Paraná", Londrina, Paraná State, Brazil, analyzed from July 1994 to April 2001. Among 39 blood donors with positive serology for HIV, 12 (30.8%) were anti-HBc positive, 10 (25.6%) for anti-HCV, 1 (2.6%) for anti-HTLV I/I, 1 (2.6%) was positive for syphilis, and 1 (2.6%) for HBsAg. Among the donors with negative serology for HIV, these markers were detected in 8,407 (10.5%), 441 (0.5%), 189 (0.2%), 464 (0.6%), and 473 (0.6%) samples, respectively. The difference was statistically significant ($p < 0.001$) for anti-HBc and anti-HCV. Although the predictive positive value for these surrogate markers were low for HIV infection, the results confirmed the anti-HBc and anti-HCV as useful surrogate markers for HIV infection thus reinforcing the maintenance of them in the screening for blood donors contributing to the prevention of the small number of cases in which HIV is still transmitted by transfusion.

KEYWORDS: Surrogate markers; Human immunodeficiency virus infection (HIV); Blood donors; Serological screening; Anti-HBc; Anti-HCV .

INTRODUCTION

In industrialized countries, the use of sensitive human immunodeficiency virus (HIV) screening tests, donor deferral, and more conservative use of blood have resulted in a dramatic decrease in the transmission of HIV infection by blood transfusion. The risk of HIV transmission in the United States by blood screened negative for HIV antibody was recently estimated at one in 440,000-660,000 donations. However, in many developing countries where the prevalence of HIV infection among blood donors is orders of magnitude greater than in industrialized countries, an estimated 5 to 10% of HIV infections are due to blood transfusion¹⁰. More strategies and measures to improve the effectiveness of the routine screening of blood donors and the safety of the blood components have been evaluated.

The rate of hepatitis B virus (HBV) infection in HIV infected patients is 10-30 times higher than in general population from United States¹⁹. During the HBV infection, the HBV produces envelope protein or surface antigen (HBsAg) in vast excess during the period before seroconversion. For this reason, antigen tests with sufficient sensitivity were available

for blood donation screening at a very early stage. With exposure to the neutralizing anti-HBs antibodies, the HBsAg disappears. The core particle of the hepatitis B virus (HBcAg) is an extremely potent antigen that elicits strong B- and T-cell responses in individuals exposed to the virus. The antibody to core antigen (anti-HBc) occurs early in acute infection, 4-10 weeks after appearance of surface antigen of hepatitis B virus (HBsAg), usually persists longer, or for lifetime, than other hepatitis B virus (HBV) markers, is associated with an elevated risk of transmission of non-A non-B hepatitis and has been used as a surrogate to screen blood donors^{14,20}. Anti-HBc was introduced in routine donor screening in 1987 in an attempt to identify donors at risk of transmitting post-transfusion non-A non-B hepatitis¹³. Anti-HBc detects persons who have been previously infected with HBV and can therefore serve as surrogate test for other infectious agents. In addition to indicating previous exposure to HBV, the anti-HBc assays have been used as surrogate marker for the presence of other infectious agents. In some blood banks in regions of high prevalence of HIV infection, the anti-HBc was implemented as a surrogate test for HIV infection⁹. Exclusion of anti-HBc positive donors reduces the incidence of post-transfusion hepatitis and possibly other virus infection, such as HIV infection, due the frequency of dual infection.

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The rate of anti-HBc among blood donors in the United States ranged from 1.0%⁶ to 1.5%⁹. The anti-HBc is present without other serologic markers and with normal alanine aminotransferase (ALT) in 2% of routine blood donors in the United States; 70% of these are due to recovery from subclinical HBV infection, and may be infectious, and the rest are considered false-positive¹⁹. In Brazil, anti-HBc and ALT were introduced in blood donor screening in November 1993¹⁴. The prevalence of anti-HBc among blood donors in Brazil ranged from 5.40% to 18.18%, according to different regions of the country¹⁴.

The discovery of hepatitis C virus (HCV) in 1989³ and the subsequent introduction of specific screening tests for anti-HCV have reduced the rate of 90% of post-transfusion hepatitis infection. The anti-HCV antibodies are detected from 12 to 20 weeks after the onset of clinical signs and symptoms. During this phase, antibodies have not yet a chance to develop, but infectious virus is already prevalent in blood¹⁴. After the discovery of the HCV, the agent of 90% of transfusional non-A non-B hepatitis, the maintenance of anti-HBc and ALT was questioned. In 1995, the National Institute of Health (NIH) of the United States recommended the maintenance of the anti-HBc test because of its potential to prevent some cases of post-transfusional HBV hepatitis, it acts as a surrogate marker for HIV infection in blood donors and could decrease the residual risk of the HIV infection transmitted by blood transfusion^{1,14}. In the absence of consistent studies that would permit the exclusion of the anti-HBc and ALT tests, many countries such as the United States, France, and Brazil have maintained these tests in the serologic screening of blood donors¹⁴.

In 1972, American institutions recommended eliminating serologic test for syphilis (STS) screening of blood donors because of its limited public health value, but the recommendation was not implemented. In 1983, the STS was reevaluated, and the Food and Drug Administration (FDA) decided to retain it because of its potential value as a marker of behavior placing subjects at risk for HIV infection. However, no large study has established that the STS is a valuable marker of HIV infection among blood donors⁶.

The human T cell lymphotropic virus I and II (HTLV I/II) can be transmitted by blood and cellular blood products, maternal milk, sexual contact and by the shared use of syringes and needles among intravenous drugs abusers¹⁸. Rates of prevalence of anti-HTLV I/II among patients with acquired immunodeficiency syndrome, homosexual men, HIV infected patients and intravenous drug users are registered^{4,18}. In this study, we evaluated the importance of surrogate markers such as anti-HBc, anti-HCV, anti-HTLV I/II antibodies, serologic test for syphilis (STS), and HBsAg for the risk for HIV infection among blood donors.

MATERIAL AND METHODS

Serum samples: This study was a retrospective evaluation of the serologic results of anti-HIV, anti-HBc, anti-HCV and anti-HTLV I/II antibodies, STS, and the presence of HBsAg obtained in 80,284 serum samples from blood donors of the Blood Bank of "Hospital Universitário Regional Norte do Paraná", Londrina, southern region of Brazil, assayed from July 1994 to April 2001.

Routine laboratory procedures: All the donations were tested for infectious diseases as required by the national advisory recommendations.

The tests performed were for anti-HBc by enzyme linked immunosorbent assay (ELISA, Abbott Laboratories and Organon Teknika), anti-HCV and HBsAg by microparticle enzyme linked immunosorbent assay third-generation (MEIA, Abbott Laboratories), anti-HTLV I/II was assayed by ELISA (Embrabio, São Paulo), screening tests for anti-HIV types 1 and 2 (viral lysate and recombinant antigens) by ELISA (Abbott Laboratories, Organon Teknika, Behring Institute, Sanofi Pasteur) and confirmatory tests (indirect immunofluorescence and/or Western Blot) supported by Laboratório Central (LACEN, Curitiba, PR, Brazil). The STS used was the Venereal Disease Research Laboratories test (VDRL, Laborclin, Pinhais, PR, Brazil).

Statistical Analysis: It was assessed the prevalence, sensitivity, positive predictive value (PPV), and relative prevalence (RP) of the surrogate markers assayed, with 95% confidence interval (CI). For the analyses of the results, the Fisher Exact Test ($p < 0.001$) was used.

RESULTS

The overall prevalence of the serologic markers assayed is shown in Table 1. Thirty-nine donations (0.05%) were anti-HIV reactive, 8,419 (10.50%) anti-HBc reactive, 451 (0.56%) anti-HCV positive, 190 (0.24%) anti-HTLV I/II positive, 465 (0.58%) STS reactive, and 474 (0.59%) HBsAg reactive.

Table 1

Overall prevalence of the anti-HIV, anti-HBc, anti-HCV, anti-HTLV I/II serologic markers, serologic tests for syphilis (STS), and HBsAg in 80,284 serum samples from blood donors of the Blood Bank of "Hospital Universitário Regional Norte do Paraná", Londrina, from July 1994 to April 2001

Serologic Marker	Number of Reactive Serum samples	% Reactivity (%)
Anti-HIV	39	0.05
Anti-HBc	8,419	10.50
Anti-HCV	451	0.56
Anti-HTLV I/II	190	0.24
Serologic test for syphilis (STS)	465	0.58
HBsAg	474	0.59

Anti-HIV: human immunodeficiency virus antibody; Anti-HBc: antibody to hepatitis B virus core antigen; Anti-HCV: hepatitis C virus antibody; Anti-HTLV I/II: human T-lymphotropic virus I and II antibodies; HBsAg: hepatitis B virus surface antigen

The results of the relationship between the anti-HIV results and the serologic surrogate markers of anti-HBc, anti-HCV, anti-HTLV I/II, STS, and the presence of HBsAg showed that among 39 blood donors with positive serology for anti-HIV, 12 (30.80%) were anti-HBc positive, 10 (25.60%) anti-HCV positive, 1 (2.60%) anti-HTLV I/II positive, 1 (2.60%) STS positive, and 1 (2.60%) HBsAg positive. Among the blood donors with negative serology for anti-HIV, these markers were detected in 8,407 (10.50%), 441 (0.50%), 189 (0.20%), 464 (0.60%), and 473 (0.60%) of samples, respectively. The difference was statistically significant ($p < 0.001$) for anti-HBc and anti-HCV, as determined by the Fisher Exact Test (Table 2).

The sensitivity, PPV and RP of the surrogate markers assayed for anti-HIV results are summarized in Table 3.

DISCUSSION

The anti-HBc reactivity obtained in this study (10.50%) was higher when compared to that reported in blood donor screening surveys in the United States^{6,9,19}, and to the seroprevalence of Brazil (average 8.65%), but was lower than the rate of 14.06% registered among donors from the southern region of Brazil¹⁴. The other overall prevalence rates of the serologic surrogate markers for anti-HIV, anti-HTLV I/II, HBsAg, and STS were higher when compared with the rates of five blood centers within the United States and previous reported^{6,9}. The rates of anti-HCV and HBsAg were lower when compared with the rates registered among Brazilian blood donors (1.22% and 0.97%, respectively)¹⁴. Among the 39 anti-HIV seropositive donations, 12 (30.80%) were anti-HBc reactive, which means that the sensitivity of anti-HBc in detecting an anti-HIV

seropositive donation was 30.80%. A total of 8,407 donations were anti-HBc reactive but not anti-HIV seropositive, corresponding to a PPV of 0.10% (95% CI = 0.10 to 0.30%). The RP was 3.8, indicating that the prevalence of anti-HIV positive results among anti-HBc reactive donations was 3.8 times greater than that of anti-HIV-positive results among anti-HBc nonreactive donations. The prevalence of infection with hepatotropic viruses in an anti-HIV-reactive population from Argentina, South America, was investigated and the results showed that the rates of anti-HBc, HBsAg and anti-HCV (58.50%, 14.50% and 58.50%, respectively) were significantly higher in anti-HIV-positive patients than in the control group (3.20%, 0.50% and 1.00%, respectively), confirming the high prevalence of HBV and HCV infections in HIV-positive patients due to the occurrence of a common epidemiologic factor for the acquisition of these viruses⁵.

Numerous reports have shown the importance of the maintenance of anti-HBc in the routine of blood donor screening to help reduce the risk of post-transfusion HBV infection and to serve as a surrogate marker for HIV due to the overlapping epidemiology of HBV and HIV infection^{1,11,12,17}. During the evaluation of the risk of post-transfusion infectious diseases¹⁷, it was verified that 6 donations made before anti-HIV was detected were not used due the positivity of other serologic surrogate markers such as elevated ALT (one donation), the presence of HBsAg (one donation), anti-HBc reactivity (two donations), and auto-exclusion (two donations). However, the maintenance of this test in routine donor screening has been discussed in numerous studies. One of them¹³, reported that 34.40% of donations were positive for anti-HBc, but all of them were negative for HIV antigen p24. Moreover, 148 donors had repeat testing for p24 6 to 8 months later and all remained negative. When tested for anti-HBs, 95.70% were positive, indicating a state of acquired immunity. The other 4.30% negative for anti-HBs all tested negative for HBV-DNA and probably represented false-positive results, a phenomenon well described with available anti-HBc tests. The results indicated that adding the anti-HBc test to routine donor screening would be unlikely to further reduce the risk of post-transfusion HBV and/or HIV infection¹³.

The detection of anti-HBc reaction alone could be interpreted in several ways, such as a false-positive result as a consequence of passive transfer of antibodies from blood transfusion, the window period of HBV

Table 2

Prevalence of the surrogate markers anti-HBc, anti-HCV, anti-HTLV I/II, serologic test for syphilis (STS) and HBsAg in anti-HIV reactive and anti-HIV nonreactive serum samples from blood donors of the Blood Bank of "Hospital Universitário Regional Norte do Paraná", Londrina, Brazil, from July 1994 to April 2001

Surrogate marker	Anti-HIV+ (n = 39)		Anti-HIV - (n = 80.245)		p* value
	n	%	n	%	
Anti-HBc	12	30.80	8,407	10.50	<0.001
Anti-HCV	10	25.60	441	0.50	<0.001
Anti-HTLV I/II	1	2.60	189	0.20	0.088
STS	1	2.60	464	0.60	0.203
HBsAg	1	2.60	473	0.60	0.206

p value according to Fisher Exact Test (p<0.001); Anti-HIV +: human immunodeficiency virus antibody reactive; Anti-HIV -: human immunodeficiency virus antibody nonreactive; Anti-HBc: antibody to hepatitis B virus core antigen; Anti-HCV: hepatitis C virus antibody; Anti-HTLV I/II: human T-lymphotropic virus I and II antibodies; STS: Serologic test for syphilis; HBsAg: hepatitis B virus surface antigen.

Table 3

Sensitivity, positive predictive value, and relative prevalence of serologic surrogate markers for anti-HIV obtained in serum samples from blood donors of the Blood Bank of "Hospital Universitário Regional Norte do Paraná", Londrina, Brazil, from July 1994 to April 2001

Serologic surrogate marker	Sensitivity ^a (%)	95 % Confidence interval	Positive predictive value ^b	95 % Confidence interval	Relative prevalence ^c	95 % Confidence interval
Anti-HBc +	30.80	17.50 - 47.70	0.10	0.10 - 0.30	3.80	1.90 - 7.50
Anti-HCV +	25.60	13.60 - 42.40	2.21	1.10 - 4.20	60.70	29.80 - 123.80
Anti-HTLV+	2.60	0.10 - 15.10	0.50	0.0 - 3.30	11.10	1.50 - 80.40
STS ^d +	2.60	0.10 - 15.10	0.20	0.0 - 1.40	4.50	0.60 - 32.80
HBsAg+	2.60	0.10 - 15.10	0.20	0.0 - 1.40	4.40	0.60 - 32.20

a: % of reactive serologic surrogate marker donation among HIV-seropositive donations; b: % of HIV-positive donations among reactive serologic surrogate marker donations; c: Positive predictive value divided by %age of HIV-positive donations among negative serologic surrogate marker donations; d: Serologic test for syphilis +: positive

infection, when anti-HBc is the only serologic marker detecting current or past HBV infection^{7,8,16}, and in cases of HVB variants when it is not possible to detect the presence of HBsAg¹⁴.

As regards anti-HCV, among 39 anti-HIV-seropositive donations, 10 (25.60%) were anti-HCV reactive, which means that the sensitivity of anti-HCV in detecting an anti-HIV-seropositive donation was 25.60% (95% CI = 13.60 to 42.40%). There were 441 donations that were anti-HCV reactive but not anti-HIV seropositive, resulting in a PPV of 2.21% (95% CI = 1.10 to 4.20%). The RP was 60.70, indicating that the prevalence of anti-HIV-positive results among anti-HCV-reactive donations was 60.7 times higher than that of anti-HIV-positive results among anti-HCV nonreactive donations.

STS in screening of blood donors has been maintained, in part, to identify and remove from the blood supply donations from persons at risk for HIV infection. Some authors related that the STS could indirectly prevent the residual risk of HIV transmission¹⁵. However, other studies demonstrated a low PPV of the STS for the HIV infection (0.06%), suggesting that this screening prevents the transfusion of few HIV infectious window-period donations⁶. Our results did not show the importance of STS as a surrogate marker for HIV infection. Its sensitivity was 2.60% (95% CI = 0.10 to 15.10%), PPV was 0.20% (95% CI = 0.0 to 1.40%), and RP 4.5, which means that the prevalence of anti-HIV-positive results among STS-reactive donations was 4.5 times higher than that of anti-HIV-positive results among STS-nonreactive donations. These results confirmed that the STS screening is a poor marker and a costly strategy for preventing post-screening HIV infections and other blood-borne diseases, preventing the transfusion of few HIV infections window-period donations².

Although the present results for anti-HTLV I/II were not statistically significant for its use as a surrogate marker for HIV infection, the RP obtained of 11.10 (95% CI = 1.50 to 80.40%) indicated that the prevalence of anti-HIV-positive results among anti-HTLV I/II-reactive donations was 11.1 times greater than that of anti-HIV-positive results among anti-HTLV I/II nonreactive donations.

HTLV I/II share the same modes of transmission and risk factors as HIV. Thus, an overlap in exposure to these retroviruses is expected. The evaluation of the seroprevalence of HTLV I/II infections and their risk factors in HIV-seropositive individuals in Santos, São Paulo (Brazil) revealed an independent association of HTLV I/II infection with intravenous drug use and HCV seropositivity and the results indicated that HIV-infected individuals are at high and similar risk to be exposed to HTLV I/II infections⁴.

The low PPV obtained for all the surrogate markers for HIV infection evaluated is explained in part by the low rates of seroprevalence of this retroviral infection (0.05%) among the blood donors included in this study. Other factors could be the sensitivity and the specificity of the methods assayed to detect the surrogate markers. Lack of specificity in the detection of these surrogate markers for anti-HIV creates significant numbers of false-positive results and contributes to the low VPP, resulting in problems for the donor and blood banking community, such as unit loss, donor loss, unnecessary apprehension, and medical follow-up for the donors. Although the predictive positive value for these surrogate markers were low for HIV infection, the results confirmed the anti-HBc

and anti-HCV as useful surrogate markers for HIV infection and reinforcing the maintenance of them in the screening for blood donors contributing, in part, to the prevention of the small number of cases in which HIV that is still transmitted by transfusion. The results also reinforce the importance of the clinical and laboratory follow-up of the blood donors with reactivity of these surrogate markers, even without symptoms, in order to detect other infectious agents. As regard to HIV infection, efforts should be focused on other strategies to reduce the risk of post-transfusion of this retroviral infection. The introduction of HIV p24 antigen tests and the nucleic acid amplification techniques such as the polymerase chain reaction, are suitable methods to close the diagnostic window in blood donation screening. The introduction of these new tests in the routine serological screening also in developing countries, should be possible to increase the sensitivity of HIV diagnosis so that fewer donations will be overlooked in the diagnostic window phase and, in this way, the effectiveness of blood donor screening and the safety of the blood components will be significantly improved.

RESUMO

Avaliação dos marcadores indiretos na infecção pelo vírus da imunodeficiência humana (HIV) entre doadores de sangue do hemocentro do "Hospital Universitário Regional Norte do Paraná", Londrina, PR, Brasil

Este estudo avaliou a utilidade dos testes sorológicos para pesquisa de anticorpos anti-antígeno "core" do vírus da hepatite B (anti-HBc), anti-vírus da hepatite C (anti-HCV), anti-vírus linfotrópico de células T humanas tipos I e II (anti-HTLV I/II), testes sorológicos para sífilis e pesquisa do antígeno de superfície do vírus da hepatite B (HBsAg) como marcadores sorológicos indiretos do risco de infecção pelo vírus da imunodeficiência humana (HIV) em 80.284 amostras de soro de doadores de sangue do Hemocentro do Hospital Universitário Regional Norte do Paraná, Londrina, do período de julho de 1994 a abril de 2001. Entre 39 doadores de sangue com sorologia positiva para HIV, 12 (30,8%) apresentaram anti-HBc, 10 (25,6%) anti-HCV, 1 (2,6%) anti-HTLV I/II, 1 (2,6%) sorologia reagente para sífilis, e 1 (2,6%) a presença de HBsAg. Entre os doadores com sorologia negativa para HIV, estes marcadores foram detectados em 8.407 (10,5%), 441 (0,5%), 189 (0,2%), 464 (0,6%), e 473 (0,6%) amostras, respectivamente. A diferença foi estatisticamente significativa ($p < 0,001$) para anti-HBc e anti-HCV. Embora o valor preditivo positivo para estes marcadores para a infecção pelo HIV foi baixo, os resultados confirmam a importância do anti-HBc e o anti-HCV como marcadores indiretos úteis da infecção por HIV em doadores de sangue e reforçam a sua manutenção na triagem sorológica dos doadores de sangue contribuindo para a prevenção do pequeno número de casos em que o HIV é ainda transmitido por transfusão.

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