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Original Article

Screening blood donors by nucleic acid amplification technology in Turkey

Mehmet Özdemir[1], Uğur Tüzüner[1], Bahadır Feyzioğlu[1], Mahmut Baykan[2], Bülent Baysal[2]

[1]Department of Medical Microbiology, Medical Virology Division, Meram Medical Faculty, Necmettin Erbakan University, Konya, Turkey; [2]Department of Medical Microbiology, Meram Medical Faculty, Necmettin Erbakan University, Konya, Turkey

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Abstract: Volunteer blood donors are screened for hepatitis B virus (HBV), hepatitis C virus (HCV), and human immunodeficiency virus (HIV) infection by various immunoassay methods in Turkey. The risk of enzyme immunoassay (EIA) negative and positive nucleic acid amplification technology (NAT) samples is not clearly understood yet. The purpose of this study is to screen for such donors in Turkey by a commercially available multiplex NAT test. All donors were screened by EIA and then NAT was performed on pools of six blood sera. When NAT reactive pools were determined they resolved to test the single donation samples. Single donor positive NAT sera were discriminated by polymerase chain reaction (PCR)-based diagnostic assay (*COBAS AmpliScreen, Roche, USA).* Incompatible sample results with EIA and NAT were searched with additional serologic and confirmatory tests. A total of 3000 donors were screened and detected seronegative, 9 HBV NAT cases (0.3%) and 1 HCV (0.03%) and 1 HIV NAT case (0.03%) were detected positively. Follow-up these donors were showed that the HCV yield case was a window period and all HBV NAT yield cases were occult carriers. The use of NAT will detect occult HBV and reduce window period in HCV. The yield rate, especially in occult HBV, was higher than that in non-endemic countries like Europian countries. Therefore, for routine donor screening by NAT will be provided safer blood transfusion in Turkey cost-effectively.

Keywords: Blood donor, HCV, HBV, HIV, NAT

Introduction

Transfusion-transmitted infections (TTI) are a global public health problem. Three most important agents (Hepatitis B, hepatitis C and human immunodeficiency viruses) were responsible for these infections. It is currently estimated that about 350 million people worldwide are chronically infected with Hepatitis B Virus (HBV), 170 million with Hepatitis C Virus (HCV) and about 37 million people are living with Human Immunodeficiency Virus (HIV) [1-3]. Blood safety critically depends on suitable donor selection, detailed clinical examination for signs and symptoms of past or present infections and exception of those who represent a risk of transmitting these infections to the blood receivers. This selection relies either on predonation interviews or on laboratory screening (serological or nucleic acid amplification test (NAT)) [4]. However, despite an increase in sensitivity with this screening, there is still some residual risk that the donated blood may be contaminated by an infectious agent. The quantification of residual risk is an important part of blood safety policies worldwide [5]. Detection of these viruses by conventional serologic tests relies on the production of viral specific antibodies or viral antigen (for HBV). The production of detectable levels of antibody or antigen occurs several weeks after the early infection. During this interval, also known as the serologic window period (WP), the presence of virus in the blood of the infected individual may cause TTI. At this time although the serological test is negative. NAT methods are able to detect some cases during the serologic WP. NAT is also useful (for HBV) for detecting chronic carriers with low level viremia and undetectable levels of hepatitis B surface antigen (HBsAg) [6].

Occult hepatitis B virus infection (OBI) has been described as the existence of HBV DNA in the

Table 1. The results of blood samples detected by NAT

Blood Samples	HBsAg	Anti-HCV	Anti-HIV	HBV DNA	HCV RNA	HIV RNA
1	N	N	N	<20 IU/ml	N	N
2	N	N	N	<20 IU/ml	N	N
3	N	N	N	<20 IU/ml	N	N
4	N	N	N	<20 IU/ml	N	N
5	N	N	N	22 IU/ml	N	N
6	N	N	N	<20 IU/ml	N	N
7	N	N	N	<20 IU/ml	N	N
8	N	N	N	6080 IU/ml	N	N
9	N	N	N	4770 IU/ml	N	N
10	N	N	N	N	16 IU/ml	N
11	N	N	N	N	N	22 IU/ml

N: negative.

absence of detectable HBsAg with or without anti-HBV antibodies [7]. This phenomenon is becoming increasingly recognized in several clinical settings worldwide [8]. Several studies on blood donors using NAT confirmed this phenomenon. In many developed countries OBI formed the basis of mandatory NAT for transfused blood units [9].

The major objective of this study was to determine the prevalence of window case and OBI with NAT that were missed by serologic screening in the Turkish blood donor population.

Material and methods

Between the date of April 2010 and July 2010, a total of 3.000 unscreened, voluntary donor samples from the Necmettin Erbakan University Meram Medical Faculty Blood Center were tested. Additional blood samples from blood donors for the study were taken into EDTA tubes (*Becton Dickinson, France*) and were centrifuged at 14,000 rpm for 30 minutes. All samples were routinely screened by Enzyme Immunoassay (EIA) method for HBsAg (*Murex HBsAg v3.0, Abbott Diagnostics, Dartford, UK*), anti-HCV (*Murex anti-HCV v4.0, Abbott Diagnostics, USA)*, anti-HIV 1 and anti-HIV 2 (*Murex HIV 1.2.0, Abbott Diagnostics, USA).*

Blood donors samples which were negative screening test results were studied in mini-pools on the Cobas s 201 system (*Roche Molecular Diagnostics, USA).* The system is used for resolution testing of reactive pools and to identify the reactive individual specimens. The reactive primary pools were further resolved by testing the six individual donations that made up the pool. The identification of the viral agents in the positive specimen was verified by the COBAS AmpliScreen tests for HBV, HCV, and HIV-1, with the multiprep extraction method. COBAS AmpliPrep (*Roche Molecular Diagnostics, USA)* was carried out by using automatic extraction kit, by the recommendations of the manufacturer of the device.

A run was represented by five positive kit controls, a negative kit control, and 1 to 18 pools of six samples. A run was considered complete and valid if all the kit control was valid. If any controls within a run were invalid, the entire run was invalid. A run could also be invalidated if an instrument error occurred during the processing of the run. An invalid test was defined as the pool that did not result in a valid test outcome on a valid run. For a sample to have a valid, non-reactive test result, the associated internal control had to be valid; for a sample to have a valid reactive test result, the associated internal control could be either valid or invalid.

Quantitation range of the method for HBV is 20 IU/mL-1.7E+08 IU/mL, for HCV, it is 15 IU/mL-1.0E+08 IU/mL, and for HIV-1 it is 20 IU/mL-1.0E+07 IU/mL.

Donor samples with discordant results between the multiplex test and the serologic tests of record were retested with samples taken directly from the plasma unit. Confirmatory tests for HBV, HCV, and HIV were performed with HBsAg neutralization test *(PRISM, Abbott Diagnostics, Chicago, USA*), and anti-HIV-1 and -2 western blot respectively.

Results

For the donor testing, two versions of computer software (*Amplilink, Roche, USA)* were used to operate the COBAS Ampliscreen instrument and the COBAS TaqMan analyzer. No cross-contamination was observed when HBV, HCV, and HIV-1 samples of high titer were pooled and tested on the cobas s 201 system. In this study, we collected 3.000 donations that made up 500 pools. A total of 11 pools (2.2%)

were initially positive. Of these, 11 reactive donations were resolved by individual tests (**Table 1**).

Among 3.000 seronegative donations, 9 HBV NAT yield cases (0.3%) and 1 HCV (0.03%) and 1 HIV NAT yield case (0.03%) were detected. Follow-up results showed that the HCV yield case was a WP and all HBV NAT yield cases were occult carriers. It was decided that HIV yield case was a false positive result.

Discussion

In our country, after a thorough history and physical examination, blood donors currently are screened for HBV, HCV and HIV infections, with determining of HBsAg, anti-HCV and anti-HIV parameters. Since 2014, the Turkish Red Crescent began using NAT testing in some centers. NAT assays are usually done to decrease the risk of TTIs; nonetheless, they are also useful to detect the specificity of serologic screening tests. An increase in screening test sensitivity of TTIs is highly desirable to supply recipient safety. But in societies with low prevalence rates, the positive predictive value is comparatively poor [10-12]. Increases in the overall HIV, HCV and HBV incidence rates during the NAT screening period may be a result of higher NAT sensitivity compared with serological testing [13].

NAT assays based on searching the viral genome by RT-PCR method in mini pools [14]. Pool formats are used for the number of samples ranging from 16 to 96. Nucleic acid amplification method was not applicable due to cost in small pools and individual blood donors. Liu et al. have lowered the pool volume which is for screening like the small pools of 20 donations, to increase the sensitivity of the test system [15]. In another study from Japan, while 50 sample pool NAT prepared for HBV were negative, 20 sample pool NAT were positive [16].

To increase the sensitivity of NAT methods is needed preparation of the pool with a large volume of sample. Number of samples to be kept low in order to prevent the effects of dilution, it is not recommended to prepare for the larger pool from 25 samples [15-20].

Transfusion transmission of HBV infection constitutes 5-11% of post-transfusional infections. Low levels of HBsAg carriers, which has negative serologic test like WP, can cause TTIs [21].

The possibility of post-transfusion hepatitis B for each blood and blood products recipient is 2/10.000. HBV developed hepatitis after transfusion rate is 0.3-1.7%. This rate is up to 10% in some publications [22-24].

There are studies in Turkey with molecular methods that screening for HBV DNA level in blood donors. A study conducted in Turkish Red Crescent Blood Centre in June 2007 and September of 2008, 12.852 HBsAg negative blood donor screened by the method of individual donor nucleic acid testing (ID-NAT) (*Tigris-Chiron, USA*) and 0.047% of samples HBV DNA level was found positive [25]. Kemahlı et al. were detected two HBV DNA positive samples (0.03%) of his study in 7.372 HBsAg negative blood donors [26]. Bal et al. were found one HBV DNA positive (0.012%) sample while working in 8.333 transfusion [27]. A total of 4.352 HBsAg negative volunteer-donors in ages of 18-65 years were included in the another study from Turkey. The samples of the donors were tested with RT-PCR in order to detect HBV DNA. Following HBV DNA screening, only two positive serum results were found. Test was repeated on two positive samples with both the same and an alternative method. Repeated tests resulted negative; therefore all samples were assessed as HBV DNA negative. In all samples of HBsAg negative donors from two different centers, HBV DNA was found to be negative [28].

Another study, on screening 21.115 donors for HCV; on pilot tube and repeat plasma bag testing by ELISA, 83 donors (0.39%) were found reactive. 41 donors were HCV RNA reactive with ID-NAT. 37 of 41 donors were concordant reactive with ELISA [29].

The other study with 18.354 donors tested by both ID-NAT and fourth generation ELISA. At the results 7 donors were found to be positive NAT, negative ELISA for HBV and HCV. The prevalence of NAT yield cases among routine donors was 1 in 2622 donations tested (0.038%) [30].

In a study conducted by the Flichman et al. from Argentina, 2.595.852 samples tested nationwide from 2004 to 2011. One HIV RNA and one HCV RNA samples were positive in NAT assays [31].

Another study from India, 10.015 donor samples were screened by immunoassays and both versions of NAT. A total of 21 NAT yields were detected; three were positive by both NAT systems, whereas 18 samples were reactive only. NAT yields include 18 HBV (17 HBV yields were OBI and 1 was in WP) and 3 HCV (all WP infections) yields. No HIV-1/2 yield was found [32].

In a study conducted by Kumar et al, of the 32.978 samples, 43 (0.13%) were found to be ID-NAT reactive but seronegative. Out of 43, one for HIV-1, 13 for HCV and 27 for HBV were reactive by differential assays. There were two samples that were reactive for both HCV-HBV and counted as HCV-HBV co-infection NAT yield. The prevalence of these tested by ID-NAT is 0.06%, 0.71%, and 0.63% for in order of HIV-1, HCV and HBV. The combined NAT yield among blood donors was 1 in 753 [33].

The German Red Cross Blood Donor Services detected HBV, HCV and HIV-1 between 1997 and 2005 in order of 43, 23 and 7 donors using NAT. 22 out of 43 (about 50%) of these HBV infected donors were in the early infection, while 21 were OBI [34].

In an another study 10.302 donor samples were run for ID-NAT. ELISA testing was performed for HBC, HCV, HIV at the same time. Reactive samples were approved using PCR. During the study period in the 10.302 samples tested, they identified 15 NAT yields, and all these revealed HBV DNA in the factious assays. Eight of these were specific yields and the remaining cases were determined as HBV NAT yield. No HCV or HIV yields were detected during the study period [35].

113.014 donors were evaluated in another study. Prevalence of TTI was 1.38% for HBV, 0.54% for HCV, 0.27% for HIV. Compatible serologic and NAT reactive results for HBV, HCV, and HIV testing, were found in 1.643/2.480 (66.25%) positive donations. NAT yield in this study was 1 in 628 donations [36].

A study from Prague, two groups of samples were tested. In the first one, 5074 samples from sequential blood donors, and in the second one, 5 repository preseroconverted samples from repeat blood donors. One sample was found reactive by chemiluminescent microparticle immuno assay (CMIA) and NAT, 31 samples were only CMIA reactive (15 anti-HCV, 4 HBsAg, 12 anti-HIV/p24) and one pool (6 samples) was found reactive in the first group. One sample was only NAT reactive in the second group [37].

Another study from Italy, 3.894.894 blood donations were investigated for HCV RNA and 2.186.468 for HIV RNA. Of these, 12 were found to be HCV RNA positive and 4 HIV RNA positive, with an observed NAT versus antibody based assay yield of 3.1/106 donations for HCV and 1.8/106 donations for HIV, respectively. Thus the final NAT yield for HCV is 1.79/106 [38].

Worldwide, over 93 million donations made every year. Blood transfusion continues to save millions of lives each year. It increases the quality of life of patients suffering from life threatening conditions. At the same time, blood transfusion is an important mode of transmission of infection to the recipients. Transfusion safety begins with healthy donors. A fundamental part of preventing TTI is to notify and counsel reactive donors. This protect the health of the donor, prevent secondary transmission of infectious diseases to others, reduces risk of vertical transmission [39]. This study evaluated the system performance in Turkey, including sensitivity, reproducibility, cross-contamination, and test validity. At present, there are no regulations for mandatory testing of blood components for HBV DNA by NAT in the world.

The study illustrates the value of testing donor samples for both HBsAg and HBV NAT, especially donors from regions with a high prevalence for HBV. The introduction of NAT in Turkey would add an extra layer of safety to the blood supply, especially with regard to the transmission of HBV by low-level chronic carriers and the transmission of HCV by WP infection. The yield rate, especially occult HBV, was higher than that in developed, non-endemic countries. Therefore, NAT implementation for routine donor screening in a more cost-effective manner should contribute to safer blood transfusion in Turkey.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Uğur Tüzüner, Department of Medical Microbiology, Medical Viro-

logy Division, Meram Medical Faculty, Necmettin Erbakan University, Meram, Konya, Turkey. Tel: +90 3322237029; E-mail: drugurtuzuner@gmail.com

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