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Transmission of occult hepatitis B virus by transfusion to adult and pediatric recipients in Taiwan

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***Background/Aims*: The infectivity of occult hepatitis B virus (HBV), defined as HBsAg-negative but HBV DNA-positive, after transfusion has been low but not negligible. To address this, we investigated the incidence of post-transfusion HBV infection after receiving screened blood units in Taiwan.**

***Methods*: Consecutive HBV-naïve (anti-HBc-negative) recipients with normal ALT were followed for HBV DNA and serologic markers before and after transfusion. Among 4448 blood recipients, 467 (10.5%) were anti-HBc-negative. Post-transfusion 6-month follow-up was completed for 327. We identified 5 (1.5%) who developed hepatitis B viremia 1 week after transfusion. Three were children who later seroconverted to anti-HBc but with normal ALT indicating subclinical acute infection, despite all had anti-HBs from previous vaccination. One had transient transfusion-transmitted HBV without seroconversion to anti-HBc and one possibly had occult HBV infection. Our findings suggested the possibility that occult HBV infection was transmissible by transfusion. The incidence of post-transfusion acute HBV infection was 0.9% (100 per million units) in naïve recipients in Taiwan, a figure 7∼40-fold higher than in developed countries. Moreover, some vaccinated children with anti-HBs were still susceptible.**

***Conclusions*: Therefore, despite active immunization, sensitive screening assays for occult HBV infection such as nucleic acid amplification test could be considered in endemic areas.**

***Keywords*: Occult hepatitis B virus; transfusion; HBV DNA; anti-HBc**

1. Introduction

Blood transfusion and component therapies are well-established and essential medical practices. However, blood collected from large populations is inevitably associated with a risk of pathogen transmission [1,2]. Currently, serologic screening is the main method used to reduce the frequency of transfusion-transmitted viral infections. In western countries where the prevalence of HBV infection is low, it effectively decreases infection rates to approximately 2.5 per million

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Abbreviations: ALT, alanine aminotransferase; Anti-HBc, antibody to hepatitis B core antigen; Anti-HBe, antibody to hepatitis B e antigen; Anti-HBs, antibody to hepatitis B surface antigen; HBe, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; NAT, nucleic acid amplification test; PCR, polymerase chain reaction.

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units for human immunodeficiency virus, 9.1 to 11.1 per million units for hepatitis C virus, and 2.5 to 15.3 per million units for hepatitis B virus (HBV) [3–8]. However in hepatitis B endemic areas, using new viral detection technology especially the nucleic acid amplification test (NAT), it has been discovered that among individuals with past hepatitis B infection and seronegative for hepatitis B s antigen (HBsAg), around 3–30% actually retained viral DNA in their blood or blood cells. They have the so-called occult HBV infection [9,10]. Even among individuals positive for anti-HBs and anti-HBc, a criteria for full recovery from past hepatitis B infections, 3–15% still tested positive for HBV DNA by NAT, though at a very low titer [10–13]. It is imperative to know how often HBV DNA-positive blood from donors with occult HBV infection is transfused into recipients and what the consequences are [14,15]

From another aspect, the screening program for HBV infection among blood donors differs between developed and developing countries where prevalence of HBV infection differs greatly. In low prevalence countries, like the United States and Japan, blood donors are screened for both HBsAg and antibody to hepatitis B core antigen (anti-HBc) [5,16]. Individuals positive for either are disqualified because of ongoing or past infections. The strategy of combined HBsAg and anti-HBc screening virtually eliminates blood-transmitted HBV, with the rare exception of donations in the window-period when serological markers are still negative [1,14,17,18]. To further reduce the risk of transfusion-related infections in the window period, NAT is used to directly detect viral genomes and has already been implemented in Germany and Japan [19–26]. However, such practice is feasible in countries where overall hepatitis B infection rate is low (less than 3%). By contrast, in countries where hepatitis B is endemic, about 90% of adults may have either past or ongoing hepatitis B infections [27,28]. Combined HBsAg and anti-HBc screening strategy would disqualify most volunteer blood donors. Therefore in countries like Taiwan, blood donors are screened only for ongoing infections by HBsAg or ongoing hepatitis activity by serum alanine aminotransferase (ALT) levels, but not for past infections by anti-HBc. This strategy bears residual risk of HBV transmission. The incidence of acquiring HBV infection from these donors with occult HBV infection is likely higher than in non-endemic areas. These observations call for re-evaluation of the current protocol used to screen blood donors with occult HBV infections.

To answer these questions, we previously conducted a prospective study of post-transfusion hepatitis, and found that 2 (18%) of 11 HBV-naïve patients receiving blood from donors with occult HBV infection became hepatitis B viremic without clinical symptoms [29], but the recipient number was limited. In addition, the study only enrolled adults [29], but not child recipients who represent a different population regarding the status of HBV exposure. Most Taiwanese adults experienced HBV infections with naturally acquired anti-HBs or anti-HBc, but most children and adolescents developed anti-HBs after HBV vaccination in a national program which was launched since 1984 [27]. As they grew up, their anti-HBs titers gradually declined. Our recent study indeed showed that only less than 40% of the vaccinated adolescents retained a protective level of anti-HBs 10 years after primary vaccination [30]. It is therefore also important to know the outcome of exposure to transfused occult HBV in the vaccinated children or adolescents whose serum anti-HBs titers already decreased significantly decades after vaccination [31–35]. To address these issues, we prospectively screened anti-HBc-negative blood recipients in our hospital, followed for their post-transfusion hepatitis B status, and compared the outcomes between adults and children. Our results indicated a low, but definite, risk of transmission of occult HBV by transfusion.

2. Patients and methods

2.1. Blood recipients

From June 2001 through May 2003, we conducted a surveillance of all blood or blood component recipients in the National Taiwan University Hospital prospectively. The recipients who met the following criteria were recruited: those who were negative for anti-HBc, had normal serum ALT level (<41 U/L for males and <31 U/L for females in our hospital) before transfusion, had no previous history of liver diseases, and had no history of alcoholism, drug addiction, or exposure to hepatotoxic drugs. We recorded the causes of hospitalization and blood component replacement. The history of blood or blood component transfusion from 2 months before to 6 months after enrollment was taken as well as the history of hepatitis B vaccination.

To study post-transfusion HBV infection, recipients who were negative for serum HBV DNA were enrolled and their serum samples were collected at enrollment, and 1 week, 1 month, and 6 months after index transfusion (transfusion occurring immediately after enrollment) for serial ALT and HBV DNA analyses. Though it was best to collect the blood of all donors for study, the number was too large to be practical at this stage. We thus did not store their samples.

In recipients with detectable hepatitis B viremia 1 week after transfusion, serum HBsAg, anti-HBs, and total and IgM anti-HBc were also assayed at the aforementioned four time points.

All the blood and blood components were provided by the Taipei Blood Center, and all qualified donors were negative for serum HBsAg and had normal serum ALT level according to current screening policy in Taiwan.

Serum samples were aliquoted and kept at -70 °C until testing.

2.2. Hepatitis virus markers

Serum specimens from each recipient before transfusion were screened for anti-HBc using a microparticle enzyme immunoassay (AxSYM Systems, Abbott Laboratories, North Chicago, IL). In those anti-HBc-negative recipients who had detectable hepatitis B viremia after transfusion, serum anti-HBc at enrollment was repeated with another commercial kit (Elecsys Systems, Roche Diagnostics, IN). Sera were also tested for HBsAg, anti-HBs and IgM anti-HBc with commercially available kits (Elecsys Systems; sensitivity: 0.09 ng/mL for HBsAg) as indicated. For anti-HBs, serum titers >10 IU/L were considered positive.

2.3. Virologic assays

2.3.1. Extraction of serum HBV DNA

Serum DNA was extracted from 200 μL serum using a commercially available kit (QIAamp DNA Blood Mini Kit, QIAGEN Inc, Valencia, CA) as previously described [9].