Effect of screening for hepatitis C virus antibody and hepatitis B virus core antibody on incidence of post-transfusion hepatitis

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Since November 1989, Japanese Red Cross blood centres throughout the country have screened donors for hepatitis C virus (HCV) with an Ortho enzyme-linked immunosorbent assay for antibody to the C100-3 viral peptide. Simultaneously, the centres started to screen for units with high-titre (≥2^6) antibody to hepatitis B virus core antigen (HBcAb) in the absence of hepatitis B virus surface antigen and antibody. To test the effectiveness of this policy, the incidence of post-transfusion non-A, non-B hepatitis (PTNANBH) and post-transfusion hepatitis B (PTHB) after screening had been introduced (November, 1989, to December, 1990, inclusive) was compared with the incidence before screening (January, 1988, to October, 1989, inclusive). Incidence of PTNANBH in patients who had received 1–10 unit transfusions was 4.9% (58/1189) before screening vs 1.9% (15/784) afterwards. Incidence in those who had 11–20 unit transfusions was 16.3% (64/392) vs 3.3% (4/124). Incidence of PTHB was 0.25% (4/1597) before screening; no cases have been detected subsequently. These results show the effectiveness of the first-generation anti–HCV test and indicate the value of screening for high-titre HBcAb in addition to HBV surface antigen testing in HBV endemic areas.

Introduction

Despite screening donated blood for hepatitis B surface antigen (HBsAg) and for serum alanine aminotransferase (ALT) concentrations higher than 35 Karmen units, post-transfusion non-A, non-B hepatitis (PTNANBH) developed in 621 (18.1%) of 3437 transfused patients studied in Japan over the 11-year period 1976–1987.1 The frequency of post-transfusion hepatitis B was considerably reduced by these measures, but even so 11 cases (0.3%) were reported. The incidence of post-transfusion hepatitis B (PTHB) was 0.25% (4/1597) before screening; no cases have been detected subsequently. These results show the effectiveness of the first-generation anti–HCV test and indicate the value of screening for high-titre HBcAb in the absence of HBsAb, with subsequent elimination of these units; the aim was to reduce the incidence of post-transfusion hepatitis B further and especially to prevent the fulminant variety. We now report the results of a prospective study to assess the effectiveness of these policies.

Methods

Patients who had received blood transfusions were examined for at least 3 months post transfusion; serum ALT concentrations were determined every 1–2 weeks. Patients with known liver diseases and abnormal ALT concentrations before their transfusions were excluded. PTNANBH was diagnosed according to previously published criteria.4

The study was carried out in Kyushu University Hospital (Fukuoka), Tokushima University Hospital (Tokushima), Kinki University Hospital (Osaka), National Kanazawa Hospital (Kanazawa), Hiroshima JR Hospital (Hiroshima), hospitals in the Hachioji District (Tokyo), Tokyo Women's Medical College (Tokyo), and National Sendai Hospital (Sendai). Blood units voluntarily donated to the Japanese Red Cross blood centres in each district were tested for HBsAg by reverse passive haemagglutination. Blood units with serum ALT concentrations higher than 35 Karmen units were not used for transfusion.

To screen for HCV we used the Ortho enzyme-linked immunosorbent assay for antibody to the C100-3 peptide of the virus (Ortho Diagnostics). HBcAb was determined by the capacity of the test sera at 2^6 dilution to inhibit a limited amount of HBcAg (25 μl, 4 haemagglutination units/ml) in agglutinating erythrocytes fixed with glutaraldehyde and coated with anti-HBc.2 HBcAb was determined by passive haemagglutination. Standardised kits for testing HBsAg, HBcAb, and HBsAb were prepared by Japanese Red Cross blood centres.

Results

908 cases were followed up after screening began (November, 1989–December, 1990, inclusive). The results were compared with those of 1581 cases detected before HCVAb and HBcAb screening was initiated (January, 1988–October, 1989, inclusive). It was already known that the number of units of blood transfused was an important determinant of the incidence of PTNANBH; before HCVAb and HBcAb screening was introduced, recipients of 11–20 unit transfusions were more than three times as likely to contract PTNANBH as recipients of 1–10 units (16.3% vs 4.9%). To separate the effect of screening from changes in the proportion of transfusions of 11 units or more, we therefore analysed the effect of the screening carried out since November, 1989, according to these two groups. Among patients who...
received 1–10 units, the incidence of PTNANBH was significantly reduced from 4.9% (58/1189) to 1.9% (15/784); p < 0.001 by t-test. Among patients who received 11–20 units before screening, the incidence of PTNANBH was 16.3% (64/392), and was reduced to 3.3% (4/124) after screening (p < 0.001).

Post-transfusion hepatitis B was observed in 4 (0.25%) of 1,581 patients transfused before screening. No cases of post-transfusion hepatitis A were observed after screening for HBsAg and high-titre HBCAb with negative HBsAb had started.

**Discussion**

Screening for HCVAb and HBCAb clearly contributed to the decrease of PTNANBH even though the HCVAb screening kit that we used is not sensitive enough to identify all blood units infectious for HCV. HBCAb screening was adopted as a surrogate test for preventing PTNANBH before the HCVAb screening became available in Australia and the USA. Although our aim in starting high-titre HBCAb screening was to decrease the incidence of post-transfusion hepatitis B, this strategy may also have contributed to the decrease in PTNANBH.

The reduction in the frequency of PTNANBH shows the usefulness of our screening policy; the programme is also important for the prevention of hepatocellular carcinoma, cirrhosis, and chronic hepatitis. These conditions are closely linked to PTNANBH, and, in HCV-endemic areas such as Japan, are linked especially to post-transfusion HCV infection. In the hope of providing more complete protection against post-transfusion hepatitis C, we are now investigating more sensitive screening tests with other HCV-related antigens.

With respect to HBCAb screening, Hooftnagel et al. have proposed that such screening can identify blood units infectious for HBV with undetectable levels of HBsAg. However, this policy is difficult to implement in most Asian countries since HBV infection is endemic and a large proportion of the population is HBcAb-positive. Since HBsAg negative/high-titre HBCAb units that were positive for HBV DNA by polymerase chain reaction were also related to fulminant cases of PTHB, exclusion of units with high-titre HBCAb as the only marker of HBV infection may effect more complete protection from the risk of post-transfusion hepatitis B, including the fulminant type. Fortunately, the number of such donors tends to be small, so the loss of units would not threaten the blood supply. We recommend that blood banks in HBV endemic areas should add screening for high-titre HBCAb to their existing HBsAg screening method.

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**REFERENCES**


**SHORT REPORTS**

**Production of parathyroid-hormone-related protein by cholesteatoma cells in culture**

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Specimens of cholesteatoma were removed at surgery from five patients who had evidence of bone resorption. Parathyroid-hormone-related protein (PTHrP) was detected, by radioimmunoassay, in conditioned media from keratinocyte cultures derived from all five samples. Concentrations of PTHrP in conditioned media from secondary cultures were higher for the cholesteatoma cells than for normal keratinocytes from controls matched for age and sex. Thus, production of PTHrP by cholesteatoma may be a contributory factor in the bone destruction commonly associated with this disorder.

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Cholesteatoma is characterised by the presence of a keratinising epithelium in the middle ear. It is thought to be derived from ingrowth of the migratory keratinocytes of the epidermis covering the tympanic membrane and deep external ear canal. Although the pathogenesis is not fully understood, the disorder is commonly associated with severe localised bone loss, the epithelium being separated from bone by a layer of inflammatory granulation tissue. The factors causing the bone loss remain unknown. Few studies have examined the possibility that the cholesteatoma produces factors which promote bone resorption. Instead, research has concentrated on theories of pressure necrosis and cellular/biochemical reactions associated with the inflammatory tissue.