Blood Transfusion and Infectious Diseases

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Makoto HANDA

Associate Professor, Blood Center, Keio University School of Medicine

Abstract: In Japan, drawing a lesson from the spread of AIDS and hepatitis C transmitted through blood transfusion, antibody screening was established, followed by the introduction of nucleic acid amplification testing for HIV, hepatitis B virus, and hepatitis C virus. The safety of donated blood has increased dramatically, but there remains the threat of a new variant Creutzfeldt-Jakob disease while bacterial infection is the most urgent practical issue. Management of in-hospital collection of allogeneic blood components and storage of autologous blood is left to each facility, and the risk of transmission of infectious diseases exists. As professionals dealing with blood, which can cause infectious diseases at any time, we should be fully aware of the risks involved and exercise constant caution.

Key words: Blood transfusion; Posttransfusion hepatitis; HIV; Bovine spongiform encephalopathy

Introduction

Many pathogens and pathogenic agents are transmitted via blood, causing infection. Because infusion of blood or its components into the body, or blood transfusion, imports a much greater amount of infectious agents into blood vessels compared with an accidental needle prick, it is one of the medical activities involving the highest risk of infection (Fig. 1). Major disasters such as drug-induced AIDS and hepatitis C have been caused by blood transfusion at the hospital. Thus medical professionals must always question the safety of donated blood, which is medical society’s fundamental resource affecting the nation’s health and welfare significantly. Blood transfusion should be considered a daily medical activity containing the risk of nosocomial infection.

Transfusion-Transmitted Infectious Diseases

Infectious agents transmitted by blood include hepatitis viruses; syphilitic spirochete; retroviruses such as adult T cell leukemia viruses (HTLV-I/II) and AIDS viruses (HIV-1/2); viruses found in the ordinary environment such as EB virus and cytomegalovirus, which cause asymptomatic infection in many humans; and emerging infectious disease pathogens found in certain areas of some countries other than...
Japan, such as malaria parasite and *Trypanosoma cruzi*, which causes Chagas’ disease (Table 1).

Although not definitely reported, the following organisms are also highly likely to cause infection through blood: tropical hemorrhagic fever viruses such as Ebola virus; Borna disease virus, which is an animal encephalitis virus often found in patients with schizophrenia or depression; and Lyme disease-inducing spirochete (*Borrelia*) transmitted by mites.

New variant Creutzfeldt-Jakob disease (nvCJD) resembling bovine spongiform encephalopathy (BSE), which caused panic in Britain and other European countries and has recently been a significant problem in Japan as well, may be transmitted by abnormal prion proteins, the causative agents of the disease, through blood transfusion. The possibility is now being studied.

1. **Hepatitis**

Japan’s transfusion medicine has been a battle against hepatitis. Surprisingly, half of the transfusion recipients had contracted hepatitis because of paid blood donation before a blood donation system was introduced in 1964. Blood came to be supplied totally by donation in 1969 after a six-year transition period, when the incidence rate of posttransfusion hepatitis dropped to 16.2 percent. Then examination of the hepatic function by GOT and GPT and detection for HBs antigen of hepatitis B virus (HBV) were included in the screening of donated blood, reducing the rate to 14.3 percent. After 400 ml blood donation and blood component collection started under the revised standards for blood collection in 1986, the rate further dropped to 8.7 percent. In 1989, detection for anti-HBc and anti-hepatitis C virus (HCV) antibodies started, lowering the rate to 2.1 percent. Finally, the rate dropped below 0.48 percent after the initiation of the second generation of tests for anti-HCV antibody in 1992.\(^1-^3\)

However, because of the nature inherent in antibody detection, a few cases were still reported of the development of hepatitises B and C caused by blood donated during the period between infection and antibody development (the window period). Then a screening technique for detecting the viruses themselves at a high sensitivity using nucleic acid amplification testing (NAT) was developed in Japan. This was applied first to mini-pools of samples of plasma derivatives for fractionation along with testing for HIV in 1997; then to 500-sample mini-pools of blood preparations for transfusion in October 1999; and to 50-sample mini-pools in February 2000.\(^3-^5\)

As a result, of the 11,488,868 units of donated blood having passed biochemical and serological tests, 200 were found HBV-positive, 41 HCV-positive, and 4 HIV-positive by October 2001. This translates to the prevention of infec-
tion by the introduction of NAT in 20 cases, 5 cases, and 2 cases, respectively, of the estimated 1.29 million patients receiving blood transfusions annually. This indicates the safety level of the blood preparations for transfusion currently used.

Despite these efforts, cases of posttransfusion hepatitis not of the type A, B, or C occur. Some may be caused by liver-affinitive viruses such as hepatitis G virus (HGV or GBV) or TT virus. Ten to twenty percent of patients receiving frequent blood transfusions or chronic dialysis possess anti-hepatitis G virus antibody compared to 1.7 percent for healthy blood donors. Thus, it seems certain that the virus is transmitted by blood. However, the pathogenicity is still unclear.

2. Retroviruses

Testing for anti-HTLV-I and anti-HIV-1 antibodies was included in the screening of donated blood in 1986, and testing for anti-HIV-2 antibody was added in 1994. In western Japan, the proportion of HTLV-I carriers was as large as 1 percent of the population and the rate of infection due to blood transfusion was nearly 10 percent. However, the horizontally infected through blood transfusion rarely develop viral diseases such as leukemia, lymphoma, or neurological symptoms, suggesting that the introduction of antibody detection has assured an almost satisfactory level of safety.

HIV infections have a great impact on society partly because of the poor prognoses for the infected. As stated above, multiple reports of HIV infection through blood donated during the window period led to the introduction of NAT for HIV along with two types of hepatitis viruses. However, it should be noted that the window period exists even with NAT.

3. Parvovirus B19

Parvovirus B19, the cause of epidemic erythema infectiosum, has affinity for red blood cells and causes pure red cell anemia. In patients with chronic anemia such as congenital hemolytic disease, this virus may aggravate the condition. It may also have significant effects on embryos and newborn infants. A large proportion of adults have acquired the antibody to this virus through asymptomatic infection. Therefore screening for the antigen of this virus was introduced to blood donation in 1997, thus assuring safety almost completely.

Because it has no envelope, this virus is resistant to inactivation treatment by heating or solubilizers. Therefore, it can be transmitted by plasma derivatives. Actually, imported derivatives not made from blood donated in Japan were recently found to cause infection at a high rate. In a prospective study of 85 pneumectomy patients receiving local treatment with imported fibrin sealant, viral DNA was detected and transient reticulocytopenia was observed postoperatively in 6 out of 29 patients (20.7 percent) preoperatively antibody negative. This suggests that the establishment of safety standards for imported derivatives is imperative and that those derivatives must be used with caution.

4. New variant Creutzfeldt-Jakob Disease (nvCJD)

Since the first case of nvCJD was found in Britain in 1994, more than 100 cases in Britain, 3 in France, and 1 in Ireland have been observed. This disease bears striking clinical and pathological similarities to BSE (mad cow disease), which occurred explosively in Britain prior to nvCJD, and characteristically develops in the young generation. Thus, this was named nvCJD in order to distinguish it from the original isolated CJD. Like scrapie in sheep or kuru stemming from the cannibalism of the aboriginal people of New Guinea, the body of infection of nvCJD is abnormal prion agents. An epidemiological study strongly suggested that patients had been infected with this disease across the species barrier by ingesting tissues of BSE-infected cows. Infection is completed in the lymphatic tissue of the intestinal tract. The possibility has been shown that prion agents may
be accumulated in lymphocytes, particularly the dendritic cells of lymph follicles, and travel all over the body.9)

By 2000, the British government took measures to remove white blood cells from all donated blood before storage while importing all plasma derivatives, for which removal and inactivation of prion agents are difficult, from other countries. Yet whether nvCJD is transmitted by blood remains unclear. Because the incubation period for this disease lasts long, it is possible that many people in the period donate blood. Then immeasurable damage to the nation by blood transfusions is anticipated. Therefore, other European and American countries employed similar policies on the handling of blood. In fact, when sheep were transfused with blood from other sheep that had ingested brain tissues of BSE-infected cows, one sheep developed encephalopathy similar to mad cow disease.10) This result strongly suggests the possibility of infection of this disease through blood transfusion, and accumulation of stronger evidence is expected.

In Japan, would-be blood donors are interviewed to exclude people who have spent a certain period of time in European countries, such as Britain or France, where nvCJD and BSE are occurring. However, if BSE goes widespread, Japan may also have to consider adopting those measures that European countries were quick to employ.

5. **Bacterial Infection**

The safety of blood preparations now seems to be almost perfect against known pathogens that can be detected by screening. Currently the most worrying type of infection is infection with bacteria mixed into blood preparations. Nevertheless, this problem is overlooked or underestimated in Japan. Actually, 1 out of 2,000 units of platelet preparations stored at room temperature is contaminated with bacteria, and it is estimated that more than 150 deaths resulting from those contaminated preparations occur annually in the United States.11)

For red blood cell (RBC) preparations, which are stored at low temperature, the psychrophilic bacteria *Yersinia enterocolitica* and *Serratia* pose a threat while for platelet preparations stored at room temperature, indigenous bacteria on the skin including *Staphylococcus epidermidis* are a problem. The highly deadly *Yersinia enterocolitica* contamination is caused by blood from donors with transient bacteremia. It is considered to take three weeks or more of storage for the bacterium concentrations to reach a noxious level. In consideration of the risk, storage of RBC preparations (RBC MAP) is limited to three weeks in Japan though they could be stored for six weeks. Cases of posttransfusion sepsis from platelet preparations are sporadically reported in Japan, and investigation of the conditions is imperative. Depending on the results, manufacturers may be required to perform screening, as some of their European and American counterparts do now.

**Problems**

1. **In-hospital allogeneic blood collection**

As stated earlier, blood preparations derived from donated blood collected and processed by the Japanese Red Cross Blood Center for general use are satisfactorily safe thanks to their great efforts. However, many medical facilities still use allogeneic blood collected at the site. Such blood should not be used except in a disaster emergency or when the stock of blood has run out, because blood collected at the hospital can never be guaranteed the safety comparable with the safety of donated blood due to the capability of performing infection screening tests such as NAT. There is no doubt about the relative benefits of using donated blood to the recipient. It should not be allowed if consent to blood transfusion is obtained without informing the patient of this point.

Recently the Japan Society of Blood Transfusion submitted “Guidelines on Collection, Process, and Use of Blood and Its Components
Intended for Treatment at Medical Facilities” to the Ministry of Health, Welfare and Labour. Guidelines on the handling of blood and its components at medical facilities will be published soon.

2. Autologous blood and nosocomial infection

Informed consent to blood transfusion has become required, and use of autologous blood during elective surgery has become common. The duration of preoperative blood storage sometimes extends to six weeks, and there is concern about contamination with bacteria such as *Yersinia enterocolitica*. Therefore, special caution should be exercised to prevent nosocomial infection. The present conditions need to be reviewed and autologous blood should be collected and stored at a dedicated administrative section following the procedures prescribed in the Guidelines on Autologous Transfusion (the Japan Society of Blood Transfusion and the Japan Society of Autologous Transfusion, revised in January 2001). Autologous blood transfusion, which should be far safer than allogeneic blood transfusion, should be re-evaluated. Of course, medical professionals should be careful in handling autologous blood of patients with infectious disease in order to protect themselves.

**Conclusion**

Blood preparations for transfusion made from donated blood; plasma derivatives such as albumin; allogeneic blood, and autologous blood collected at the hospital; and blood components such as hematopoietic stem cells also collected at the hospital—any of these materials is not free from the risk of infection. As professionals dealing with them, we should be always cautious, understanding the level of the risk. Blood could cause infectious diseases at any time and it is an important object of risk management in the hospital. It is important to implement blood management centered around the director of a dedicated administrative section under consensus of the whole facility (the committee on transfusion therapy).

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