

# Transfusion-transmitted infections in hemophilia patients who underwent surgical treatment: a study from a single center in north China

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## Abstract

**Introduction:** Transfusion-transmitted infections (TTIs) continue to be a major challenge among hemophilia patients. This study was conducted to investigate the prevalence of TTIs including hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus (HIV) and syphilis in patients with hemophilia who received surgical treatment due to bone or joint lesions in the Department of Orthopedics.

**Material and methods:** The present study was conducted from July 1996 to November 2016 in Beijing, China. A total of 189 patients who underwent orthopedic procedures were enrolled. Blood samples were obtained from the patients and were tested for hepatitis B surface antigen (HBsAg), hepatitis C virus antibody (HCV Ab) and human immunodeficiency virus antibody (HIV Ab).

**Results:** Among 189 hemophilia patients included in the study, 54 (28.6%) tested positive for TTI. Seroprevalence for HBsAg was found in 8 (4.2%) cases, HCV Ab in 48 (25.4%) cases, HIV Ab in 2 (1.1%) cases, and syphilis in 1 (0.5%) case. No statistically significant difference in the numbers of patients with positive HCV Ab was seen between hemophilia A (26.0%) and B (20.0%) ( $p = 0.786$ ). The seroprevalence of HCV Ab (12.1%) in 66 hemophilia patients diagnosed after 1995 was significantly lower than that (32.5%) among hemophilia patients diagnosed before or in 1995 ( $p = 0.003$ ).

**Conclusions:** Though few patients have become positive for HBsAg and HIV Ab, HCV is still the major virus of concern for hemophiliacs who have undergone orthopedic procedures. Hepatitis B vaccination should be given to the high-risk population including hemophilia patients as soon as possible.

**Key words:** transfusion-transmitted infections, hemophilia, surgical treatment, orthopedics.

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## Introduction

Hemophilia is an X-linked recessive, inherited bleeding disorder arising from a deficiency of coagulation factor VIII in hemophilia A (HA) or factor IX in hemophilia B (HB) [1]. The prevalence of hemophilia A is estimated to be 1 in 5000–10 000 males [2], while hemophilia B affects approximately one in 25 000–30 000 males [3]. According to the degree of deficiency of the clotting factor, patients are classified as having mild, moderate or severe hemophilia [4]. The bleeding episodes of hemophilia are treated with replacement therapy including fresh frozen plasma (FFP), cryoprecipitate and blood-derived and/or recombinant factors. However, multiple blood

transfusions and replacement therapy have been linked to a high risk of transfusion-transmitted infections (TTIs), especially viral infections such as hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus (HIV) and syphilis [5–8]. The problem of TTIs is more serious in the developing countries due to the lack of a strict regime for the screening of blood and its components prior to transfusion. Clotting factor concentrate is the preferred treatment option. In China, the majority of hemophilia patients do not always have recombinant or highly purified plasma-derived factor concentrates for prophylaxis and management of bleeding disorders due to their high cost, and for them blood transfusion with FFP or cryoprecipitate or even allogeneic blood transfusion remains the mainstay of management. Thus the chances of getting any of these viral infections increase with the number of blood transfusions.

Patients with hemophilia tend to present with recurrent bleeding of varying severity that occurs spontaneously or post-traumatically into joints, muscles or organs [9]. Hemarthrosis is considered the most common clinical manifestation of the disease, which can lead to hemophilic arthropathy, mainly affecting the elbow, knee and ankle [10]. Hemarthrosis results in progressive degradation of articular cartilage that can lead to permanently deformed and crippled joints [11]. This is associated with significant disability and impairment of quality of life. Hemophilia has been considered to be a relative contraindication to surgical treatment. However, with factor replacement therapy, most surgical and invasive procedures, including major orthopedic procedures with restoration of joint function, could be performed safely in patients with hemophilia since 1998 in our ward. Main concerns about TTIs in hemophilia patients requiring surgery not only include the significantly higher operational risks compared with other patients, but also the potential occupational exposures of the health care professionals, especially to HIV infection. To our best knowledge, there have been no reports about the prevalence rates of TTIs among such a special population.

The aim of this study was to investigate the prevalence of TTIs including HBV, HCV, HIV and syphilis in patients with hemophilia who received surgical treatment due to bone or joint lesions in the Department of Orthopedics, Peking Union Medical College Hospital (PUMCH).

## Material and methods

### Patients

The present study was conducted from July 1996 to November 2016 in the Department of Orthopedics, PUMCH, Beijing, China. The inves-

tigation was carried out in accordance with the Declaration of Helsinki for human research, and the protocol was approved by the Ethics Committee of PUMCH. Informed consent forms prior to enrolling in the study were obtained from all adult participants, parents, or legal guardians. All patients with hemophilia who underwent elective procedures including joint arthroplasty, joint fusion, open reduction and internal fixation (ORIF), soft tissue release or hemophilic pseudotumor resection were included.

The clinical data collected included age, sex, family history, type of coagulation disorder in hemophilia patients, types of blood products used in the treatment of hemophilia (whole blood, FFP, cryoprecipitate and clotting factor concentrate), units of blood products transfused, types of surgery and HBV vaccination status.

### Laboratory assays

Blood specimens were collected from a total of 189 patients. Serum samples were separated from the whole blood, aliquoted and stored at 70°C until they were tested. All sera were screened for hepatitis B surface antigen (HBs Ag), hepatitis C virus antibody (HCV Ab) and human immunodeficiency virus antibody (HIV Ab) with enzyme-linked immunosorbent assay (ELISA) using a fully automatic biochemical analyzer (Abbott Laboratories, USA). Syphilis serology was tested with the rapid plasma regain (RPR)-card (Hansheng Diagnostics). All samples had been submitted to our center laboratory, and the detection was manipulated according to the instructions. Positive and negative controls were set up.

### Statistical analysis

All analysis was performed using SPSS (version 17) software. The collected data were presented as mean  $\pm$  SD or number (percent). Data comparisons were performed using the  $\chi^2$  with Fisher's exact test. A *p*-value of less than 0.05 was considered to be statistically significant.

## Results

In the present study, 189 patients with hemophilia reporting a history of surgical interventions due to bone or joint lesions were enrolled. These patients have undergone 212 major orthopedic procedures including total knee arthroplasty (TKA), total hip arthroplasty (THA), TKA plus THA, hemophilic pseudotumor resection, ORIF, external fixator operation, joint fusion and soft tissue release. One hundred sixty-nine (89.4%) patients suffered from hemophilia A, and 20 (10.6%) patients had hemophilia B. All patients were male, and the mean age of the study population was

**Table I.** Replacement therapy given to patients

Types	Number of patients	Number of units transfused
Whole blood	72	996
FFP	171	4778
Cryoprecipitate	92	3368
PCC	23	414
Factor VIII concentrate	169	2835 (vials)

FFP – fresh frozen plasma, PCC – prothrombin complex concentrate.

23.2 ±17.51 years (range: 9–68 years). Thirty-one (16.4%) patients had moderate hemophilia (factor level: 1–5%), and 158 (83.6%) patients had severe hemophilia (< 1% factor level). Sixty-six patients were diagnosed with hemophilia after 1995, in which 12 patients were born after 1995. Replacement therapy given to patients is shown in Table I. The majority of patients were treated with factor VIII concentrates or prothrombin complex concentrate (PCC) and FFP (100% and 90.5%, respectively) as replacement therapy.

Among 189 hemophilia patients included in the study, 54 (28.6%) tested positive for TTI. Seroprevalence for HBsAg was found in 8 (4.2%) cases, HCV Ab in 48 (25.4%) cases, HIV Ab in 2 (1.1%) cases, and syphilis in 1 (0.5%) case. These two (1.1%) HIV-infected patients were positive for HCV Ab as well. The patient with positive serology for syphilis (0.53%) was also positive for HCV Ab, and serologic evidence for both HBV and HCV infection was observed in 2 (1.1%) patients. One hundred and sixty-one subjects were vaccinated against HBV during their lifetime.

We found HCV Ab positive in 44 (26.0%) patients with hemophilia A and 4 (20.0%) patients with hemophilia B. No statistically significant difference in the numbers of patients with positive HCV Ab was seen between the two types of hemophilia ( $p = 0.786$ ). Out of 66 patients with hemophilia diagnosed after 1995, 8 (12.1%) are HCV Ab positive, while 40/123 (32.5%) diagnosed before or in 1995 are HCV Ab positive. The prevalence of anti-HCV seropositivity was significantly higher among the hemophilia patients who were diagnosed before or in 1995 ( $p = 0.003$ ).

## Discussion

According to the Annual Global Survey 2015 published by the World Federation of Hemophilia, China ranked third in the world after the United States and India, having the largest number of hemophilia cases. Currently in China, there are about 13 624 patients with hemophilia at a prevalence of 1.0 per 100,000 population [12]. Surgery may be needed for associated complications of hemophilia, such as severe arthropathy with fixed flex-

ion and other deformities of knees, ankles, and elbows [13]. Since the concentrates of coagulation factor VIII and IX became available, orthopedic procedures have been performed more commonly. However, for hemophilia patients receiving surgical treatment, exposure to blood products was even higher. TTIs continue to be a serious problem for the management of hemophilia patients in developing countries. This study showed the seroprevalence of TTIs including HBV, HCV, HIV and syphilis among hemophilia patients who underwent orthopedic procedures. We found that the seroprevalence in this special population is 54 out of 189 (28.6%). The factors associated with TTIs mainly include prevalence of these infections in the general population, a poorly organized system of blood screening and transfusion, and low sensitivity of pathogen-testing technologies [14].

HCV remains a major infection of concern in hemophilia patients, which can progress to chronic hepatitis, liver cirrhosis, and hepatocellular carcinoma [15]. As there is currently no effective vaccine available to prevent hepatitis C, epidemiological surveillance for HCV is critical. In this study, the prevalence of positive HCV Ab among 189 hemophilia patients was reported to be 25.4%. FFP was used in 90.48% of cases, cryoprecipitate in 48.68% and whole blood in 38.10%. The route of HCV transmission is therefore highly likely to be transfusion related. Evidence indicated that seropositivity for HCV was significantly associated with a longer history of blood transfusion [16]. In China, HCV Ab in donor blood was detected officially in 1993; thus some hemophilia patients might be infected with HCV from transfused blood or blood products without anti-HCV screening. Also, the major method to screen blood donations for anti-HCV antibodies is ELISA, which cannot exclude a potentially infectious window period donation. Among all blood donors in mainland China from 1990 to 2010, prevalence of HCV has been reported to be 8.68% [17]. The prevalence rate seems to be high among our blood donors. In general, a high prevalence of HCV in the blood donors was associated with a high prevalence among multi-transfused patients.

Our study also found that the seroprevalence of anti-HCV antibodies (12.1%) in 66 hemophilia patients diagnosed after 1995 was significantly lower than that (32.5%) among hemophilia patients diagnosed before or in 1995 ( $p = 0.003$ ). It might be related to the more stringent management of blood products after 1995, when the Ministry of Health stipulated a conversion from manual to automated plasma collection that helps reduce cross-contamination risks. It may also be associated with strict screening of blood donors, elimination of blood donors with positive HCV-Ab and application of lyophilized human coagulation factor VIII preparations.

In this study, HBsAg positivity, a marker of active HBV infection, was reported to be 4.2% among 189 hemophilia patients, which is lower than that of HCV infection. The low prevalence in our patients might be due to mandatory HBV screening in blood donors and the introduction of the HBV vaccination program in 1992. However, performing a highly sensitive HBsAg test does not eliminate the risk of hepatitis B transmission. This may be attributed to occult HBV infection, the inability to detect HBsAg using ELISA techniques in the window phase or other transmission routes, such as healthcare-associated infections. In our study, all participants had a history of surgical procedures. As shown in an epidemiological serosurvey of hepatitis B in 2006, a prevalence of 7.18% was reported [18]. This prevalence rate is higher than that among the hemophiliacs in our study. It might be related to the vaccination against HBV for newborns and the high-risk population such as hemophilia patients, and mandatory HCV screening for blood donors. The majority of our patients (85.2%) were vaccinated against HBV, and all of them were seronegative for HBsAg. It seems that hepatitis B vaccination in patients with hemophilia to decrease HBV prevalence was successful.

HIV accelerates fibrosis progression among HCV-infected patients. HCV/HIV co-infected patients exhibit more rapid progression of liver disease than HCV mono-infected patients [19]. In our study, only two (1.1%) HCV/HIV co-infected patients were detected. As shown in official statistics from the United Nations Program on HIV/AIDS (UNAIDS), HIV/AIDS prevalence in China was reported to be 0.037% of the total population at the end of 2014 [20]. HIV infection is not a significant problem in the Chinese population of hemophilia patients due to the relatively low prevalence of HIV in the general population and HIV screening for all blood donations since 1998. In the study, only 1 (0.53%) hemophilia patient was positive for syphilis. Transfusion-transmitted syphilis does not represent a major hazard of modern blood transfusion therapy.

So far, many studies have been conducted to investigate the prevalence of viral infections in hemophilic patients worldwide. The reported prevalence of infections varied in different geographical regions. The rate of HCV seropositivity among Iranian hemophiliacs was in a wide range between 8.57% and 98% [7, 21–26]. The lowest rate was in West Azerbaijan (8.57%) [21] and the highest in Isfahan (98%) [22]. HCV infection in Birjand of Iran (20%) was similar to our rate [23]. In Iran, the prevalence of HBsAg shows low levels from 0% to 2% lower than our finding [7, 21–25], and HIV infection ranges from 0% to 4.7% [21, 23–26]. The reported prevalence of HIV in Hamedan Province of Iran (1.1%) was similar to our results [24]. The difference observed in hemophiliacs from different cities in Iran may be due to selection methods and laboratory methods.

The prevalence of infections in different countries was also varied. In Western India, Mittal *et al.* found that 10 (12.5%) were infected with TTI among 80 multiply transfused hemophilia patients. Seroreactivity for HCV was seen in 7.5% of cases and HBV in 5%. No patient was found reactive for HIV and syphilis [27]. A study conducted among 173 multitransfused male hemophiliacs in Karachi, Pakistan by Borhany *et al.* showed that 51.4% were seropositive for HCV, 1.73% for HBV and none of them for HIV Ab [28]. In a cross sectional study during 2002–2003 on multi-transfused patients in Honduras conducted by Vinelli and Lorenzana, 1.6% of hemophilia patients were positive for HBsAg and 26.9% for HCV Ab [29].

In conclusion, though few patients have become positive for HBsAg and HIV Ab, HCV is still the major virus of concern for hemophiliacs who have undergone orthopedic surgery. The strategies to reduce the risk of acquiring TTIs appear to be successful. Hepatitis B vaccination should be given to the high-risk population including hemophilia patients as soon as possible.

### Conflict of interest

The authors declare no conflict of interest.

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