

# Vaccination Against Hepatitis A for Hemophilic Patients: Is It Necessary?

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## Abstract

**Background:** Hemophilic patients require long-life intravenous infusion of factor concentrates to treat bleedings. This could increase the risk of transmission of blood-borne infections like hepatitis C.

**Objectives:** The current study was aimed at investigating the immunity status against hepatitis A in hemophilic patients in south Khorasan and evaluating the necessity of hepatitis A vaccination for this population.

**Patients and Methods:** A cross-sectional descriptive study was conducted between 2014 and 2015 on all hemophilic patients of south Khorasan province, Iran (n = 108) for anti-HAV total, anti-HCV, HBS-Ag, anti-HIV, and anti-HTLV-1/II. Note that no one had already received a hepatitis A vaccine.

**Results:** As our results show, 77.8% of the participants (59% under 20 and 88.4% above 20 years old) were seropositive for anti-HAV total; 20.4% and 2.8% (three patients) of the cases were anti-HCV positive and anti-HTLV-1 positive, respectively, while none of the subjects were HBS-Ag or HIV-Ab positive. Seventeen of the patients (15.75%) showed a co-infection of HAV with HCV, and five HCV-infected patients (22.73%) had no immunity against hepatitis A. There was a significant relationship between age, rural life, and anti-HAV positive state in our patients ( $P < 0.001$ ). No significant relationship between positive anti-HAV status and sex ( $P = 0.16$ ), severity of hemophilia ( $P = 0.23$ ), and infection with HIV, HCV, HTLV-1, and hepatitis B ( $P > 0.05$ ) was detected.

**Conclusions:** More than 40% of the hemophilic patients under 20 years of age in the present study had no immunity against hepatitis A, and 23% of hepatitis C patients had not had a hepatitis A co-infection yet. Since hepatitis A can show a fulminant course in hepatitis C patients, vaccination against hepatitis A seems necessary in hemophilic patients in the region.

**Keywords:** Prevalence, Hepatitis A, Viral Infections, Hemophilia, Hepatitis C

## 1. Background

Hepatitis A virus (HAV) infects 212 million people each year, including 55 million symptomatic cases and 35,245 deaths (1). The virus (HAV) is a member of the Hepatovirus genus of Picornaviridae family. HAV is a non-enveloped, linear, single-stranded RNA virus (2, 3). The lack of a lipid envelop allows the virus to be thermostable and acid resistant and resist bile lysis, which facilitates efficient fecal-oral transmission (4).

Thus, due to improvements in socioeconomic status, sanitation, accessibility to clean water, and the introduction of effective immunization programs, a dramatic decline in the endemicity of HAV has occurred in many parts of the world over the past few decades (5, 6). A significant declining trend in age-specific seroprevalence has been found in Italian people under 30 years of age (61% in 1988, 33% in 1995, and 8.9% in 2005 - 2008). Other

studies in Taiwan and Brazil have shown that the prevalence of anti-HAV has decreased to a very low level in recent years (7, 8), although most developing countries have shown an increasing trend in the age groups of  $>$  or  $=$  21 years old (9-11). Further, some serious disease patients, for instance hemophilic patients, still need more intensive care. These patients require a long-life intravenous infusion of factor concentrates to treat bleeding. This could increase the risk of transmission of blood-borne infections through HAV-contaminated blood along the fecal-oral route in hemophilic patients because blood products are inactivated by solvent-detergent purification (12, 13).

Such HAV infection outbreaks that occurred among hemophilic patients between 1989 and 1997 worldwide have stimulated researchers to reconsider the safety of plasma derivatives because the non-enveloped viruses are neither easily inactivated by the heating technology that

has been used since 1980 nor by the solvent-detergent inactivation procedures being used today (12). Therefore, both the American academy of pediatrics (AAP) and the centers for disease control (CDC) strongly recommend an HAV vaccine for persons with clotting-function disorders (10).

Although prevention programs have been performed in Iran in recent years, no data about the prevalence of the disease are available to prove their success. Therefore, a selective screening strategy in at-risk people, hemophilic patients as an example, with identifiable risk factors has been advocated, and neonates of known HAV-positive patients have been demanded to possibly fill informational gaps in the disease prevalence (4) and, thus, to evaluate the effectiveness of prevention programs (8).

## 2. Objectives

The study's objective was to determine the seroprevalence of hepatitis A viral antibody in hemophilic patients and to document the transmito-epidemiological correlates of blood that are anti-HAV positive.

## 3. Patients and Methods

A cross-sectional descriptive study was conducted from April 2014 to April 2015 on all hemophilic patients in south Khorasan province, Iran. Those who were willing and eligible to participate in the study, not having been vaccinated against HAV, were interviewed and informed of the research aim. Having given consent, 108 of the patients were recruited and formed the research subjects. They were evaluated with respect to viral safety, sex, blood group, and the origin of the clotting factor concentrates, categorized into three groups (10-17, 18-27, and [U+O2C3] 28), similar to the study of Mauser-Bunschoten (14). The study was performed under the supervision of Birjand University of Medical Science and was approved by the local ethics committee of the university hospital.

### 3.1. Assays

All 108 serum samples were tested with enzyme immunoassay (EIA) kits (Abbott-hepatitis A virus AB META-AXSYM system, Germany) for total anti-HAV antibody. Hepatitis B surface antigen (HBsAg) (Enzygenost® HBS Ag, USA), anti-hepatitis C virus antibodies (HCV-Ab) (Anti-HCV ELISA, DRG Co., Germany), anti-human immunodeficiency virus antibodies (HIV-Ab) (Genscreen HIV; Bio Rad®, France), and anti-human T-cell lymphotropic virus- antibodies (HTLV- Ab) (Gene labs® Diagnostics HTLV-, Switzerland) were evaluated. All positive sera in HCVAb were confirmed by a nested reverse transcriptase (RT-PCR) test (Disorine® HCV-RNA, Spain). Note that all blood products,

in Iran, have carefully been screened for hepatitis C virus since 1996 (15).

### 3.2. Data Management and Statistical Analysis

Fisher, X<sup>2</sup> and T-test were performed with the confidence of 95% using SAS program (version SAS 9.1.3 Service Pack 4, Copyright (c) 2002-2003 by SAS Institute Inc., Cary, NC, USA). Clinical and virological data collected in separate databases were coupled after insuring anonymity.

## 4. Results

This study included 108 patients with hemophilia in south Khorasan province. The mean age of participants was  $27.7 \pm 16.4$  years, with a minimum of 4 and maximum of 85 years old; 0.93.5% (101 cases) of patients were males and 6.5% (7 cases) were females. In addition, 53% of our cases were single and 47% were married; 86% of these patients had hemophilia type A (Table 1). The severity level of hemophilia in 7.4% was mild (clotting factor level: 5% - 25% of normal), in 7.4% was moderate (clotting factor level: 1% - 5% of normal) and in 85.2% was severe (clotting factor level: less than 1% of normal) (16). Further, the blood group in 38% of patients was B, in 28% was A, in 25% was O, and only 9% had blood group AB. Moreover, 34% of our cases lived in urban areas, while 66% were from rural areas.

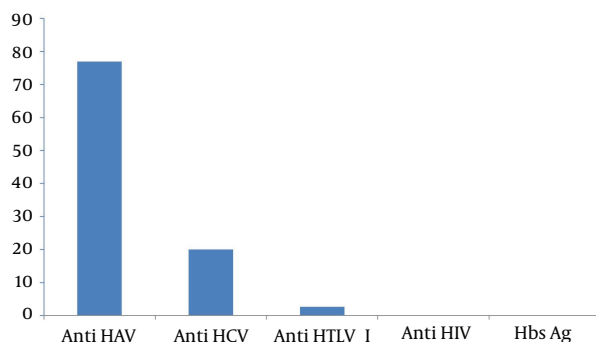
**Table 1.** Distribution of Patients Regarding the Type of Hemophilia or Hemorrhagic Disorder

Type of Hemophilia	Frequency, %
Hemophilia type A	93 (86)
Hemophilia type B	2 (1.9)
Von vill brand disease	4 (3.7)
Other	9 (8.4)
Total	108 (100)

In this study, 77.8% of the cases (84 out of 108) were anti-HAV antibody seropositive. Of the subjects who were under 20 years old, 59% were HAV-positive were, while this percentage was 88.4% for those over 20 years old ( $P < 0.001$ ).

Anti-HCV antibody positive was detected in 20.4% of cases (22 out of 108), of which 82% (18 of 22) were HCV-RNA positive. Three hemophiliacs (2.8%) were anti-HTLV-1 positive, whereas none of the cases were HBS-Ag or HIV-Ab positive (Figure 1). Co-infection of HAV and HCV was reported in 17 subjects (77%), and five HCV-infected patients (23%) had no immunity against hepatitis A.

There was a significant relation between age and anti-HAV positive status in our subjects ( $P < 0.001$ ), and rural



**Figure 1.** Rate of Blood Serological Markers in Blood Samples

life was also identified as a significant risk factor. However, the correlation of anti-HAV positive with sex ( $P = 0.16$ ), severity of hemophilia ( $P = 0.23$ ), and infection with HIV, HCV, HTLV-1, and hepatitis B ( $P > 0.05$ ) was not significant.

## 5. Discussion

This clinical-based report presents the burden of HAV and other blood-borne infections in a population of hemophiliacs, a high-risk population in south Khorasan province, Iran that had not been studied previously. We conducted a cross-sectional study of recent anti-HAV seroprevalence to establish effective preventative measures for HAV infection in hemophiliacs.

The overall prevalence of hepatitis A infection in the hemophilic population was 77.8%, which is in contrast with previous observations reported in Egypt (12). The rate of prevalence, however, varies widely in different parts of the world (12, 17). In a study on 133 hemophilic cases, Molina found that it was 43% among Spanish hemophilic patients (18). Mauser-Bunschoten in his study in the Netherlands showed that the anti-HAV prevalence in 197 hemophiliacs (treated with clotting factor concentrates produced from large plasma pools) was 20%, and in 144 patients (treated with small pool cryoprecipitate) it was 13% (19), while it was 22.4% in Hayashi's study in Japan (20). The level of hygiene in different communities could be one of the most important reasons for these variations. Poor hygiene, poor water sanitation, and family crowding, which increase the chance of close contact with the virus, are several reasons for the increased prevalence of the infection. Although in a cross-sectional study conducted among 1- to 15-year-old children, no difference in the seroprevalence of hepatitis A related to age groups, mean age, sex, and family size was observed (21), in most multivariate analyses, region, age group, marriage, referral date, and level of parental edu-

cation were associated with hepatitis A virus seropositivity (17, 22-29).

The outcome of the positivity rate for anti-HAV concerning region (51.4% in urban areas and 91.5% in rural areas) is completely in favor of the findings of Taghavi and his colleagues in Shiraz showing the high frequency of HAV-positive individuals living in rural areas (95.9% of rural people in comparison with 85.1% of the urban population) (28). In another study, the overall seroprevalence of HAV in the general population of three provinces of Iran (Tehran, Golestan and Hormozgan) was 86%, with no variation between the two genders (22). The prevalence in younger subjects and in urban populations was under 70% (22), while in another province of Iran (Kashan) only 3.9% of children between 1 and 15 years old were reported to be seropositive (21).

Patients' age is the other contributory factor. There was a direct relationship between seroprevalence and age, as a rise in age caused an attendant increase in seroprevalence. The other point worth noting was the significant difference between the age groups ( $P < 0.001$ ). The infection rate in subjects over 19 years old was 77.1%, while it was only 22.9% in those younger than 19. In Hayashi's study, the infection incidence in the age range of 10 - 19 years was 21.4%, and 30.8% of hemophilic patients were 40 - 49 years old (20). In Chambost's investigation, 20% of people were 30 to 35 years old, and almost 49% of infected patients were over 50 years (28).

Some reports have indicated an increasing rate of acute HAV infection in adults in Iran in recent years (23). A serosurvey in Tehran in the late 1970s found that more than 90% of 10 years old had immunity against HAV (24). Studies in the 2000s show a much lower seroprevalence in the majority of children and teenagers, while they still remain susceptible to hepatitis A infection (25), which can be one of causes of high seroprevalence. The other underlying cause is the high anti-HAV seroprevalence rate in the Middle East (26), which could increase the chance of exposure to the virus, leading to high seroprevalence in Iran.

Hepatitis C and HTLV-1 positivity were reported among 20.4 and 2.8% of our participants, respectively, similar to recent studies in Iran and the United States, where blood transfusion was reported as a common factor of HCV (30-32). The prevalence of hepatitis C infection in hemophilia patients in a study in Germany was 98.6% (33); it has also been reported to be 54.5% in India (34) and 96.97% (Mzandaran province) (30) and 60.2% (Tehran province) (35) in Iran. The seroprevalence of HCV and HBs-Ag, as the Zahedan hemophilia center reported, was 29.6% and 4.9%, respectively, in hemophilic patients (36), which is more prevalent than our study.

However, as the results of this study indicate, there

were no HIV- or hepatitis B-infected patients among the participants. The prevalence of hepatitis B infection in Borhany's study conducted in Karachi was reported to be 1.73% of hemophilic people (37); however, in another study in Iran, no association between HBV infection and blood transfusion, as a main route of infection in hemophiliacs, was reported (38).

One possible explanation for the inconsistency between the previous results and the present findings is that most of our hemophilic patients were living in rural areas and did not have access to coagulation factors in these areas; therefore, they have received cryoprecipitate instead of coagulation factors, which reduced the likelihood of blood-disease transmission. Cryoprecipitate is prepared from the blood of local blood donors, and the prevalence of blood-borne diseases such as AIDS, HCV, and HBV infection is lower in these areas. Therefore, the prevalence of infection with hepatitis C, hepatitis B, and HIV in our study was lower than previous studies. These findings support previous results from a study in south Khorasan (39).

We attempted to determine whether vaccination against hepatitis A in hemophilic patients in south Khorasan is necessary. The results show that more than 40% of the hemophilic patients in our study under 20 years of age have no immunity against hepatitis A, and 23% of hepatitis C patients have not had a hepatitis A co-infection yet. Since hepatitis A can show a fulminant course in hepatitis C patients, vaccination against hepatitis A seems necessary in hemophilic patients in the region. Moreover, further studies on hemophilic patients in other regions of Iran seem necessary to determine their immunity status against hepatitis A.

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## Footnotes

**Authors' Contribution:** Study concept and design: Masood Ziaee; acquisition of the data: Jamal Mirzaei; analysis and interpretation of the data: Seyed Ali Farsad; drafting of the manuscript: Mohammad Fereydooni; critical revision of the manuscript for important intellectual content: Masood Ziaee; statistical analysis: Gholamreza Anani Sarab; administrative, technical, and material support: Mohammad Reza Rezvani Khorashad; study supervision: Masood Ziaee.

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