

Hepatitis B virus infection in Iran; Changing the epidemiology

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INTRODUCTION

Hepatitis B virus (HBV) infection is the main cause of chronic liver disease in Iran (1,2). The epidemiology of HBV infection in Iran has been changed during the last two decades (1) and infantile vaccination with high coverage is the main cause for this change (3,4). The prevalence of hepatitis B surface antigen (HBsAg) in the country was reported between 2.5% and 7.2% in 1979 (5). It was estimated that there were one million HBsAg positive carriers among 35 million Iranians at that time (5). In the 1980s, almost 3% of the Iranian population was affected, differing from 1.7% to 5% in different provinces (1,2).

It was estimated that over 35% of Iranian have been exposed to the HBV and about 3% were chronic carriers (5). In a study performed on 250,000 healthy volunteer blood donors in Tehran, 3.6% of male and 1.6% of female donors were HBsAg carriers (6). The prevalence rate of HBsAg positivity is low now, with HBsAg carrier rate about 2% (7). In general population, this prevalence was 1.7% and 2.49% (8) in 1992 and 1993, respectively. Another study showed that HBV prevalence is 1.07% in blood donors in Shiraz in 2000 (9). The reported prevalence, ranging from 1.7% in Fars Province to over 5% in

Sistan-Baluchistan (10). Fifty-one to 56% of Iranian cirrhotic patients were hepatitis B surface antigen (HBsAg) positive (11,12). A recent study showed that the rate of hepatitis B carriers varied between zero and 3.9% with an average of 1.7% (13). HBV prevalence has decreased dramatically in Iranian population during the last decade. Improvement of the people's knowledge about HBV risk factors, national vaccination program since 1993 for all neonates, vaccination of high risk groups such as healthcare workers and the introduction of disposable syringes for use in vaccinations, hospitals and clinics might justify this decrease (14).

A recent systematic review indicated that estimation of HBsAg seroprevalence in the country in the last five years based on seven provinces data was 2.14% (15). Bear in mind the importance of HBV infection in Iran, HBV vaccination has been included in the extended program of immunization (EPI) since 1993 (14). In 2002, National Committee of Hepatitis revised the program and recommended to extend HBV immunization to twenty five-year old adolescents. Thereafter, Ministry of Health and Medical Education planned to implement HBV mass vaccination campaign for adolescents who were born from 1989 to 1992 (14). The first three-round campaign of the series covering 1989-born adolescents was implemented in 2007 in Iran (16). I think reviewing the epidemiology of HBV infection in Iran with focus

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on risk factors in general population and specific groups can help the decision makers in Ministry of Health for integration of better protocol.

Prevalence of HBV infection in general population

For estimation of HBV infection in general population, a thorough review of literature was conducted and 14 studies from 7 provinces covering 40% of country population were reviewed. Studies were as follow: 3 studies from Tehran province covering the years 2001 and 2007 (17-19), 4 from Golestan province covering 2003, 2004 and 2006 years (19,20), 3 from east Azerbaijan province in 2000, 2004, and 2005 (21-23). Other studies were from Hormozgan (2006) (19), Hamadan (2003)(24), Isfahan (2006)(25), and Kermanshah (1999-2003)(26).

The range of reported HBV prevalence was wide, ranging between 1.2% and 9.7% in general population and the studies showed heterogeneity (15). The meta-analysis point estimation for HBV prevalence in I.R. Iran between years 2001-2007 was 2.5 percent (95% confidence interval; 2.0-3.1%). The distribution of HBV infection prevalence in the country showed that there are significant differences between provinces in HBV infection rates and the highest prevalence rates was

in Golestan province (6.3%; 95%CI: 3.2-9.3%) (table 1). Using survey data analysis method, the HBV infection prevalence in I.R. Iran estimated 2.14% (95%CI: 1.92-2.35%). This estimate seems to be more accurate than meta-analysis method results as explained in the methods section. The HBV infection prevalence in Iranian men and women estimated 2.55% (95%CI:2.25-2.85%) and 2.03% (95%CI:1.6-2.46%), respectively (15).

Prevalence of HBV infection in blood donors

The prevalence of HBsAg in blood donors can guide us about the epidemiology of infection in the community, but it is underestimated due to exclusion of high risk group from pool of donation (27). With introduction of HBsAg testing in bloods, donor education and better selection, voluntary tests and appropriate use of blood and blood components resulted in significant reduction of HBV infection (28,29). However, HBV infection still remains a major health problem and serious challenging in blood transfusion system, especially in developing countries (30-32). The Iranian Blood Transfusion Organization (IBTO) was founded in 1974 and it is a national non-profit organization, and the only organization responsible for collection, processing, testing and distribution of blood and blood products under supervision of

Table 1. Estimations for HBV infection prevalence in I.R. Iran and its provinces during 2001-2007

Province	Total Sample Size(s)	Province Population	Weight*	Total; % (95%CI)	Men; % (95%CI)	Women; % (95%CI)
East Azarbaijan	5320	3603456	677.34	1.3 (1.0-1.6)	1.7 (1.2-2.1)	0.8 (0.1-1.5)
Golestan	4931	1617087	327.94	6.3 (3.2-9.3)	7.3 (3.9-10.7)	5.4 (2.7-8.2)
Hamedan	1824	1703267	933.81	2.3 (1.6-3.0)	2.2 (1.3-3.2)	2.4 (1.3-3.4)
Hormozgan	1988	1403674	706.07	2.4 (1.6-3.1)	3.1 (2.0-4.2)	1.8 (1.0-2.6)
Isfahan	816	4559256	5587.32	1.3 (0.5-2.1)	ND***	ND
Kermanshah	6820	1879385	275.57	1.3 (1.0-1.6)	ND	ND
Tehran	7870	13422366	1705.51	2.2 (1.9-2.5)	2.2 (1.7-2.6)	1.9 (1.2-2.6)
National	NA**	2.14 (1.92-2.35)	NA	2.14 (1.9-2.35)	2.55 (2.25-2.85)	2.03 (1.6-2.46)

* Weight: Province population/Total sample size, **N.A.: Not Applicable. *** ND.: Not Determined

Ministry of Health (MOH) and the IBTO high council (29). According to the IBTO regulation, initial reactive donations were excluded and discarded, and the positive donors were permanently rejected for further donation. Donors who were confirmed to be positive in screening tests were notified and invited for post donation counseling and follow-up, and in the case of HBsAg-positive donors the immediate family was recommended to be vaccinated.

IBTO implemented nationwide mandatory HBsAg screening of all blood donations in 1974 (29). In a recently published article (29), it was showed that the prevalence of HBsAg has changed and the trend was significant. The overall prevalence of HBsAg in Iranian blood donors in 1998 was 1.79% and in 2007 was 0.41%. The prevalence was lower in Fars province and higher in Siatn-Baluchistan (29). It is very clear that the prevalence of HBV infection has decreased in Iran during recent years (33). This decrease is related to improvement in donor selection and exclusion of high risk peoples from donation pools (27,34).

Prevalence of HBV infection in hemodialysis patients

Viral hepatitis B seems to be a major problem in hospitals and hemodialysis centers (35). With adherence to hemodialysis-specific infection-control practices and to hepatitis B vaccination, HBV infection has been controlled in some dialysis centers (36-39). Despite of control and preventive measures, viral hepatitis B still seems to be a major concern in medical centers with hemodialysis in some countries (40,41). HBV infection outbreaks still remain a major problem, specifically, when a failure in control of nosocomial infection occurs (42,43). In Iranian hemodialysis patients, the prevalence of positive HBSAg in patients on hemodialysis decreased from 3.8% in 1999 to 2.6% in 2005 (39). Hemodialysis patients are vulnerable to infection with HBV and HCV because of history of blood transfusion, frequent injections, partial

immunosuppression and history of kidney transplant. According to Iranian national guideline for prevention and control of viral hepatitis, the serologic status should be determined prior to dialysis for all patients with ESRD as well as cases with acute renal failure that seems to require hemodialysis. In Iran, implementation of universal precaution measures is mandatory in medical centers with hemodialysis facilities as a cornerstone for prevention of viral hepatitis B; moreover, machine dedication is a rule (44).

Duration of hemodialysis treatment seems to be a considerable variable for HBV infection acquiring in medical centers with HD facilities. This variable has been reported to be strictly correlated with seroprevalence of hepatitis B, demonstrating the significant risk of HBV nosocomial transmission (41,45-47). In addition, Ferriera et al. have showed that subjects on maintenance hemodialysis for more than three years had 2.6-fold (95% CI: 1.7- 4.0) higher risk of acquiring HBV infection compared to patients who had undergone hemodialysis less than 12 months (48). Hosseini Moghaddam et al. have reported a significant association between duration of being on hemodialysis and HCV infection (49), and this association may be true for HBV infection. Blood transfusion has been reported as a significant risk factor for hepatitis B in hemodialysis patients (41, 47). Ferriera et al. pointed out that patients who received blood transfusion before 1993 had a 2.3-fold greater risk of HBV positivity compared to those that were transfused after (48). Screening of blood products for HBsAg in Iranian blood banks has been contributed to reduce this risk (50). Additionally, the widespread use of recombinant erythropoietin for anemia treatment has decreased the requirement for blood transfusion in hemodialysis patients (39,51).

In endemic area, most of HBsAg positive cases in hemodialysis centers occur before initiation of dialysis (52,53). The risk of HBV infection in patients on peritoneal dialysis is much lower than

hemodialysis (53). This might be due to low level of risk in peritoneal dialysis compared to HD. Fortunately most of hemodialysis patients in Iran do not have history of intravenous addiction (IDUs) and it is a cause for lower rate of HCV and HBV infection in hemodialysis patients (54).

Prevalence of HBV infection in hemophilia and thalassemia patients

Hemophilia patients are at a greater risk of contracting all kinds of viral hepatitis especially hepatitis C because of persistent consumption of blood products (55-58). Nowadays, an effective vaccine to prevent hepatitis C is not yet available and post transfusion transmission of this virus has remained as a problem.

Whereas a number of effective strategies, including donor screening and especially viral inactivation procedures for concentrates and recently use of recombinant factor therapy, have been implemented in the world in order to prevent the transmission of viral infections due to blood or blood product transfusion. Surely the use of such strategies can reduce the prevalence of viral disease like viral hepatitis and AIDS in our hemophiliacs.

The prevalence of HBV infection in hemophilia in Iran is heterogeneous and it varies from 1.4% in Yazd (central province) (59), 2.7% in East Azerbaijan (60), 4.9% in Zahedan (61), 5% in Hamadan (62) to 26.7% in Guilan(63). In a study from Guilan province, north of Iran, 26.7% of hemophilia were positive for HBsAg and there was an inverse correlation between factor VIII & IX activity and seropositivity for HBsAg ($p<0.04$) (63).

Thalassemia is one of the most common genetic disorders in Iran (64). HCV is the main cause of chronic liver disease after control of Iron overload (65-67), but HBV infection is remains as an important hazard to the patients. The prevalence rate of HBsAg in thalassemia patients varies from zero in Yazd province (59), 1.5% in Tehran (68), 6% in Kerman (69) to 19% in Ahwaz (70). It

means that HBV remains a significant concern in thalassemia patients in Iran.

Modes of transmission

In case-control studies in blood donors some of the risk factors have been identified that should be considered for prevention strategies. In a study from Karaj, a cohort study in 2001 to 2003, with historical controls, the prevalence of HBV infection increased after 16 years old. The risk factors for chronic hepatitis B were older age, male gender, marital status, history of contact with hepatitis, extramarital sexual activity, IV-drug use, major surgery, experimental dentist visit, and some jobs (police, barber, and driver) (71). In another study, 2447 HBsAg positive blood donors from 1997 to 2000, were compared with 2425 HBsAg negative donors in Tehran. Factors predicting HBV infection included family history of hepatitis B infection, history of receiving blood transfusion, hospitalization, unsafe sex, male gender, and living in city area (72). Another study in blood donors in Qazvin revealed that close contact with an HBV infected person, extramarital sexual contact, history of sexually transmitted diseases and high risk jobs were independent risk factors for prediction of hepatitis B infection. Horizontal mode is more important than vertical transmission in this region of Iran (33). It seems that horizontal transmission of HBV is more important than vertical now (4,73) and sexual contact is the main factor (74).

I would like to mention that in our neighbor country, Pakistan, the main risk factors for HBV infections are injections, blood, sex and transmission from infected mothers to their infants. Widespread practices such as unsafe injections, improper disposal of hazardous waste, recycling of used syringes without proper sterilization, sharing of needles by injecting drug users and unsafe sex are believed to facilitate the transmission of these infections, resulting in high prevalence rates in the country (75-77). I am afraid for my country especially un-necessary injection in private clinics

and offices for vitamin injection that should be controlled and be limit by Ministry of Health in Iran.

Discussion

The HBV infection is a widely spread disease that affect large number of populations worldwide and is considered as a major public health problem in many countries. In Iran the mass vaccination program started at 1993 and reached to 94% coverage in 2005 (78) and the reported prevalence of HBV infection in Iran decreased from about 3.5% in 1990s (79,80) to 2.14% in 2000s (15). This change is significant but the mass vaccination program is supposed to have more significant decrease on HBV infection prevalence. This can be explained by increasing number of reports about HBV infection in Iran from 28 before 2000s to 236 after year 2000. This indicates that the trend to investigate on HBV infection in I.R. Iran have increased significantly about more than 8 times and this may result in less undetermined cases throughout the country and more attention to the infection. This can result in higher and obviously more accurate prevalence rates. Technology developments also provided more sensitive and accurate diagnostic tools, a fact that may explain the lower decrease trend in HBV infection rates during past decade despite mass vaccination program (14). With respect to the increment in coverage rate of HBV vaccination to adolescents, the Ministry of Health is serious to control the infection in Iran (14,16).

According to our results, it is estimated that about 1.5 million people in Iran living with HBV infection and assuming that 15% to 40% are at risk of developing cirrhosis and/or hepatocellular carcinoma (HCC) without intervention (81,82). Treatment of chronic hepatitis B with control of viremia can decrease the rate of progression and occurring hepatocellular carcinoma (83). It seems that alpha interferon can be the first choice in some

group of chronic hepatitis B and patients in advanced liver stage should receive nucleoside analogues for therapy (83-91).

It is estimated that 225,000 to 600,000 peoples are at risk of serious health problems related to HBV infection and needs immediate attention. Others are HBsAg positive carriers and this large number of carriers may lead to disseminate infection to healthy peoples vertically or horizontally. Health policy makers should indentify and control this large infection reserves and plan to reduce transmission rates to improve vaccination program efficiency. Increasing vaccination coverage rates especially in groups at high risk of being infected can be an effective plan to control transmission rates from carriers. These groups are mainly women at reproductive ages, youth and high risk job workers such as health care providers, barbers, drivers and intravenous drug abusers (92-94). It seems that there are growing evidences about vaccination in adult in Iran supported by changing of transmission route from vertical and horizontal in childhood to horizontal in adulthood due to some risk factors (4). Prevalence of HBV infection is about 25% higher in males than females (2.55% vs. 2.03%, respectively). This can be attributable to exposure to more risk factors such as job risk factors in men in community of Iran.

Blood testing for transfusion purposes reduces the risk for HBV infection and we can see this success in Iranian hemodialysis patients (39,95, 96). In addition, common erythropoietin administration provided a considerable reduction of transfusion number. Moreover, implementation of universal precaution in dialysis units as well as using dedicated machines for HBV infected patients has led to a decreasing trend of HBV infection. All factors mentioned above seem to promote the health level in medical centers with HD facilities that nowadays no significant increase is seen in the incidence of HBV infection with longer duration of being on HD. We strongly

recommend periodic surveillance of HBV infection among patients receiving medical services from centers with hemodialysis facilities. Regardless of signs and symptoms, having a high index of suspicion for viral hepatitis, specifically in this high-risk group, seems to be a cornerstone to decrease the incidence of HBV infection. Since liver enzymes are usually in normal ranges in HD cases, one should not merely pay attention to liver enzyme level in HD cases. Vaccination against HBV in all of hemodialysis patients and pay more attention regarding suitable efficacy of vaccination with periodic checking anti-HBs Ab is mandatory. The hemodialysis patients are a special group that responds less than other groups (35,97-99).

Based upon published data, prevalence of HBsAg positive cases in Guilan province was higher than other studies. Upon the results emerged from this study, we recommend that all hemophiliacs should be vaccinated against HBV and should have regular program for checking anti-HBs Ab. In thalassemia patients, integration of surveillance system for reporting the HBsAg and anti-HBs Ab periodically is recommended.

Family physicians can play an important role in educating people about the prevention of HBV infection (100). The objective to educate people and test them for hepatitis was successful through utilizing ethnic community leaders, religious organizations, health care professionals, and a collaborative health fair (101). Development of a broad based mechanism to develop a consensus on national policy positions, incorporation of appropriate guidance from the provinces, giving provinces an active participatory role in decision-making, garnering their support and clearly demarcating roles is suggested (102). Education of the public and health care providers regarding hepatitis and the importance of supportive relationships to clients seeking and receiving hepatitis screening and vaccination is recommended (103). Finally, the other risk factors such as dentistry should not be missed (104).

In conclusion, as it is aforementioned, fortunately the epidemiology of HBV infection has changed significantly and the health provider and health policy makers did their responsibility very nice. Control of main risk factors, more attention to new and emerging risk factors such as IDUs and using unsafe medical devices, more attention to health precaution in hemodialysis, thalassemia and hemophilia patients, increase the coverage rate of HBV vaccination and expanding it to 35 years, improving population awareness, large-scale surveillance data for this disease to estimate prevalence variations in each area in the country and integration a specific program for those regions are important strategies for better control of infection in our country. Another strategy is reducing the rate of HBV infection by finding the infected cases and decreasing the carriers' pool in the community and emphasizes more on vaccination of high risk group. The changing epidemiology of HBV infection in the world and in Iran is a result of global and mass vaccination programs in high risk and susceptible groups (78).

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