Management of non-responder health care workers to hepatitis B routine vaccination

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Abstract: Introdoction: Hepatitis B comprises one of the major health problems worldwide. Health Care Workers (HCW) are a group at risk for Hepatitis B Virus (HBV) infection. The aim of this study is Management of non-responder health care workers to hepatitis B routine vaccination. **Methods:** In a descriptive-analytical study conducted in the Department of infectious diseases in the University Of Medical Sciences Of Tabriz, Non-responder cases of HCWs to HBV vaccination were studied and management. **Results and Conclusions:** 36.8% of HCWs were male and 63.3% of them were female. Mean age of male HCWs was 34.05 ± 8.58 year and in female HCWs was 30.43 ± 6.15 year (P<0.001). Mean of Primary response antibody titer in male HCWs was 340.59 ± 205.15 IU/L and in female HCWs was 282.75 ± 194.22 IU/L (P=0.011). Mean of Secondary response (after one booster dose) antibody titer in male HCWs was 388.52 ± 175.25 IU/L and in female HCWs was 357.81 ± 164.24 IU/L (P=0.110). Non responder rate of HCWs for Routine vaccination (tree dose at 0,1 and 6 months) was 31(9.36%). Non responder rate of HCWs after one booster dose vaccination (after tree dose at 0,1 and 6 months) was 7(2.11%). Non responder rate of HCWs for secondary tree time (with double dose) vaccination (after tree dose at 0,1 and 6 months ± one booster dose vaccination) was 2(0.6%). This method seems best suited for routine immunization of people who give inappropriate response to routine vaccination. Those who did not respond to this method too, are recommended to be excluded from high risk activities in terms of exposure such as needle stick, and in case of any possible exposure, HBIG should be applied.
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1. Introduction

Viral hepatitis is one of the major occupational diseases among health care workers. Therefore, the only way to control the infection is application of necessary conditions to sterilize instruments, use of disposable gloves and needles, and vaccination of hospital staff to prevent the contamination (Hassel Horn, 1997).

Healthcare workers (HCWs) are more at risk of acquiring infection from their patients or transmitting various infections among their patients, or transferring their own infections to the patients. Acquisition of some of these infections causes severe illnesses, chronic diseases or hazardous complications (Jaggar, 2002; Ross, 2002). In order to reduce the mentioned transmission ways, the strict application of standard methods for preventing transmission of infection between patients and staff (HCWs) and their appropriate immunization has been recommended (Beltrami, 2000; Gerberding, 1995; Averhoff, 1998; Mahoney, 1999).

In medical-health centers, transmission of infection occurs through direct contact with blood or body fluids (surgery, laboratory staff, etc.), blood transfusion and hemodialysis (Zanetti, 2001; Koff, 2002; Williams, 2001; Brotherton, 2003).

In case of HCWs, occupational exposure is a constant and real concern, and this risk is higher in the starting years of this profession.

Incidence of new infections of HBV among HCWs has been reported 1% per year (Zimmeraman, 2003). The risk of transmission of HBV is 2,400 cases in every 1,000,000 surgeries, which is a high figure compared to HVC (140 per million) and HIV (24 million) (Koziol and Henderson, 1996). The risk of transmission of HBV from HCWs to the people is high as well (Hasselhorn and Hofmann, 2000).

Unlike HIV and hepatitis C, transmission of HBV can be prevented by vaccination (Roggendorf and Viazov, 2003). This effective and safe vaccine was introduced and approved in 1981 (Williams, 2001) and released in 1982 (Duclos, 2003).

Since 1991, injection of this vaccine in health centers became compulsory by WHO and other international organizations (Kane, 2000). This vaccine injected into the deltoid muscle in three doses and in months 0, 1 and 6 respectively (Kane, 2000), and over 95% of the recipients give a proper response to the vaccine (Roggendorf and Viazov, 2003). With HBV vaccination, percentage of carriers has been reduced from 15-20% to 1% (Duclos, 2003).

Regarding the wide range of HBV infection in the world, its serious complications and the high cost of treatment due to infection, the prevention of disease is inevitable.

As recommended by WHO, the groups at high risk, including HCWs, should be vaccinated against HBV.

After vaccination, antibodies against HBV are produced in the blood. Amount of the secreted antibodies in the blood depends on the number of vaccine doses and the rate of immune response of the body to the vaccine (Alavian, 2006).

When the antibody titer falls below 10 Miu/ml, people get susceptible, and there is a possibility that they get infected by HBV despite previous vaccination. Therefore, serologic examination of HBs Ab and determination of antibody levels at regular intervals is essential in HCWs, and in case of reduction of antibody titer, a booster dose of HBV vaccine should be administered (Marchou, 1995).

In this study, we were to evaluate the response rate of HCWs to HBV vaccination in cases with inappropriate response in terms of response to the booster dose and double dose revaccination.

2. Material and Methods

In a descriptive-analytical study conducted in the Department of infectious diseases in the University Of Medical Sciences Of Tabriz, Non-responder cases of HCWs to HBV vaccination were studied and management.

The studied HCWs are vaccinated by hepatitis B vaccine with fallowing properties (entitled EUVAX B, met the WHO requirements, made in Korea, LG life sciences company) for three doses (0, 1 and 6 months) and antibody was titrated three months after vaccination. All utilized vaccines were from one brand and all tests were performed in one laboratory.

ELISA test was used to evaluate the samples used kit in this study was the Anti-HBs kit, made by ROCHE Company entitled "COBAS". Methods of this kit was ELISA, in which ELISA micro plates in this method ELISA micro plates are covered by antigen S so that after adding serum containing antibodies against antigen S, antigens would bind with antibodies. In the next step, antigen S conjugated with peroxidase enzyme is added which attaches to the part of the antibodies not bound to antigens. Later, adding chromogene and substrate dies the solution whose color can be read by ELISA reader.

After performing tests and reading the plates by ELISA reader, standard curves were provided using standard samples. Later using these curves, the concentration of antibodies in the tested sample were calculated. Based on the instructions of the kit manufacturer, antibody level less than 10 units per mL was considered negative and amounts higher as positive.

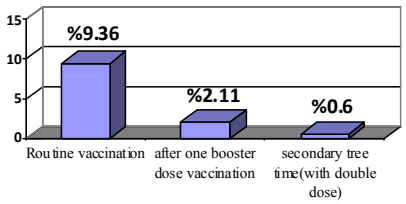
In this study, HCWs vaccinated routinely 3 times during the past 5 years on schedule (6-1-0) with negative HBcAB and HBsAg titers were studied in terms of HBsAB.

In this study, 331 HCWs were studied and those with inadequate HBsAb titers (under 10) were selected. These HCWs received a booster dose of HBV vaccine and were studied again 3 to 6 months later in the same laboratory in terms of HBsAb titers.

In this study, seven HCWs under study still had inadequate HBsAb titers.These people underwent 3-times double dose subcutaneous revaccination and 6 months after vaccination, their HBsAb titers were evaluated.

3. Results

122(36.8%) of HCWs were male and 209(63.3%) of them were female. Mean age of male HCWs was 34.05 ± 8.58 year and in female HCWs was 30.43 ± 6.15 year (P<0.001). Mean of Primary response antibody titer in male HCWs was 340.59 ± 205.15 *IU/L* and in female HCWs was 282.75 ± 194.22 *IU/L*. Mean of Primary response antibody titer in male was significantly higher than female HCWs (P=0.011). Mean of Secondary response (after one booster dose) antibody titer in male HCWs was 388.52 ± 175.25 *IU/L* and in female HCWs was 357.81 ± 164.24 IU/L.



Significant difference was not found in Secondary response (after one booster dose) antibody titer between two gender (P=0.110

Chart 1. Non Responder Rate of HCWS at tree stage of Vaccination

Non responder rate of HCWs for Routine vaccination (tree dose at 0, 1 and 6 months) was 31(9.36%). Non responder rate of HCWs after one booster dose vaccination (after tree dose at 0, 1 and 6 months) was 7(2.11%). Non responder rate of HCWs for secondary tree time (with double dose) vaccination (after tree dose at 0,1 and 6 months ± one booster dose vaccination) was 2(0.6%) (Chart 1).

Evaluation of Age, Height and Weight of HCW based on primary response antibody titer were shown in table 1. Evaluation of response to Vaccination based on Gender, Smoking and Hyperlipidemia were shown in table 2.

Table 1. Evaluation of Age, Height and Weight of HCW based on primary response antibody titer.

	Primary Response			P
	Good Responders	Low Responders	Non Responders	
Age(Year)	31.32 ± 7.02	32.65 ± 7.96	33.71 ± 8.51	0.146
Height(m)	1.64 ± .08	1.64 ± .07	1.65 ± .08	0.906
Weight(Kg)	66.28 ± 12.79	67.75 ± 14.02	69.48 ± 11.96	0.365

Table 2. Evaluation of response to Vaccination based on Gender, Smoking and Hyperlipidemia

		Sex		P	Smoking		P	Hyperlipidemia		P
		Male	Female		Yes	No		Yes	No	
Primary Response	Non Responders	10	21	0.158	4	27	0.051	4	27	0.989
	Low Responders	15	37		3	49		6	46	
	Good Responders	97	151		9	239		30	218	
Secondary response (after one booster dose)	Non Responders	3	4	0.123	2	5	<0.001	2	5	0.601
	Low Responders	4	1		2	3		0	5	
	Good Responders	115	204		12	307		38	281	

4. Discussions

In the study of Hofmann et al, 2% of female and 1.5% of male vaccinees did not develop anti Hbs and 4.8% and 7.1% respectively were low responders (anti Hbs <100 <10 IU / l) (Hofmann, 1997).

In our study, out of 31 Non-Responder HCWs in the first stage, 10 patients (32%) were male and 21 (68%) were female, that in this study, non-responsiveness was higher among females.

Ramos et al showed that 2 to 10% of healthy adults do not respond to vaccination by producing protective levels of antibody anti-HBs (assumed as protective, concentrations of ab. Anti-HBs> 10 UI / L) (Ramos, 2000).

It is unclear whether booster vaccination of non-responders offers higher anti-HBs seroconversion, and hepatitis B vaccine prevents the infection of hepatitis B mutants in healthcare workers (Chen and Gluud, 2005).

In the study of Valats et al, Up to 20% of healthcare workers are considered as non-responders to hepatitis B vaccination (anti-HBs<10 m UI/ml in serum)(Valats, 2010).

In our study, 36/9% of the cases under study were Non-Responders, similar to the results of above mentioned study.

Chlíbek et al show that the immune response decreases with increasing age (Chlíbek, 2007).

In the study of Zeeshan et al, the percentage of non responders increased gradually from 9% in participants under 25, 13% in 25-34, 26% in 35-49, and 63% in ±50 years of age(Zeeshan, 2007).

HBsAb titer in study cases was reduced by increasing weight; however, this relationship was not statistically significant. As well, mean age of the study cases was higher than the others, and this difference was not significant.

Chlíbek et al demonstrated that males achieved lower geometric mean titres (GMT) of antibodies and lower seroprotectivity rates compared to females(Chlíbek, 2007).

In the study of Zeeshan et al, male non-responders were more frequent (18%) than female ones (8%) (Zeeshan, 2007).

In our study, the rate of non-responsiveness in females was higher than in males, and after administration of the booster dose, this rate in females was higher than in males under study.

Cardell et al demonstrated that the seroconversion rate of protective anti-HBs level was 68% after 3 doses and 89% after 3 or 4 doses(Cardell, 1999).

In our study, the Good Responders after administration of 3 and 4 doses of vaccine were 74.9% and 96.4% respectively.

Factors associated with a lower response rate in the study of Cardell et al were increasing age ($p < 0.05$) and smoking ($p < 0.001$) (Cardell, 1999).
In our study, although the level of antibody titer in smokers was lower than in non-smokers, this difference was not statistically significant.

Alerany et al showed that age is the variable most closely linked to the risk of a poor immunological response (Alerany, 1993).

Yen et al demonstrated that being male, age under 40 years and positive anti-HBc are associated with non-responsiveness to HB vaccination (Yen, 2005).

Immunized workers were more protected against HBV infection than non-immunized workers, indicating that HBV vaccine was a useful measure for protection against the infection (Nagao, 2008).

Conclusions

This method seems best suited for routine immunization of people who give inappropriate response to routine vaccination.
Those who did not respond to this method too, are recommended to be excluded from high risk activities

in terms of exposure such as needle stick, and in case of any possible exposure, HBIG should be applied.

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