Long Term Immunity to Hepatitis B Vaccine Among a Sample of Secondary School Students in Damietta

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Abstract: The aim of the present study was to assess the long term immunity to hepatitis B vaccine among secondary school students aging from 15- 17 years; and to evaluate the efficacy of vaccination schedule of HBV vaccine in Egypt. **Subjects and methods:** A total number of children from 15 to 17 years (teenagers' students) in EL-Zarka district was 1106 from which 200 vaccinated children was the sample size of the study 103(51.5%) males and 97(48.5%) females .The studied students were chosen randomly from 3 secondary schools in EL-Zarka district. 118 students (59.0%) were from rural areas and 82(41.0%) from urban areas. **All included children were subjected to** complete history taking by the self-administered questionnaire, clinical examinations, and laboratory investigations (CBC, Anti HBs antibodies by ELISA and Anti HBc antibodies by ELISA). **Results:** The titer of HBsAb in 40% is less than (10IU/L) meaning loss of immunity to hepatitis B, and 59.5% of waning immunity (10-100), only 0.5% had good immunity. There was significant difference between different HBsAb levels as regard to gender distribution (i.e., gender had an effect on seroconversion of HBV vaccine). There was no effect of residence, socioeconomic status, BMI, ICU admission, feeding pattern, Hgb level and WBCs count on the seroconversion of HBV vaccine level. **Conclusion:** Hepatitis B vaccine has long lasting immunity extended to at least 15 years. No effect of urbanization, socioeconomic standards, BMI or Hgb% on level of HBsAb seroprotection.

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1.Introduction

Hepatitis B virus (HBV) is one of the most common chronic viral infections in the world. About a third of the world's population, more than 2 billion people have been infected with the hepatitis B virus **(WHO, 2009)**. The most frequent method of transmission of hepatitis B worldwide is from mother to infant **(Brook, 2002).**

Approximately 5% of all acute HBV infections progress to chronic infection, and the risk of progression from an acute to chronic phase is inversely proportional to age. Up to 90% of infants who acquire HBV infection from their mothers at birth become chronically infected. Among children who become infected with HBV between 1 year and 5 years of age, 30% to 50% become chronically infected. In adults, chronic HBV infection results in 5% of acute cases (**Helen and Donald, 2010).**

In Egypt, the estimated HBsAg prevalence is 6.7% among healthy population-based studies. Adults have a higher prevalence of 8% compared with children at 1.6%, most likely a result of the introduction of HBV vaccines for children in 1992 (**Lehman and Wilson, 2009).**

HBV vaccination is the most effective measure for prevention of HBV infection in countries with intermediate to high levels of HBV endemicity **(Puvacic *et al.*, 2004).** Hepatitis B vaccine is extremely effective in preventing vertical and household transmission. The initiation of universal vaccination of newborns in 1984 was associated with a marked decline in the prevalence of chronic HBV in children from 10% to only 0.7% within 15 years (**Landrum *et al.*, 2009).**

Two types of hepatitis B vaccine are commercially available: Plasma-derived hepatitis B vaccine and yeast recombinant hepatitis B vaccine **(Molinari *et al.*, 2007).** In Egypt, vaccination against HBV is compulsory since 1992 by three intramuscular injections into the quadriceps muscle of 0.5 ml of vaccine at age of 2,4 and 6 months (**EL-Sawy and Mohamed,2000).** Long-term protection of hepatitis B vaccine against clinically significant breakthrough HBV infection and chronic carriage depends on immunological memory, which allows a protective anamnestic antibody response to antigen challenge. Memory seems to last for up to 10-15 years in immunocompetent individuals **(Liao, 2009).**

Aim of the study

The present study was designed to assess the long ter m immunity to hepatitis B vaccine among secondary school students aging from 15- 17 years; and to evaluate the efficacy of vaccination schedule of

HBV vaccine in Egypt.

2. Subjects and methods

This study was a cross sectional study which was carried out to detect " long term immunity of HBV vaccine in sample of secondary school students '. The study was conducted during academic year 2011-2012.

Sampling: A total number of children from 15 to 17 years (teenagers' students) in EL-Zarka district was 1106 from which 200 vaccinated children was the sample size of the study 103(51.5%) male and 97(48.5%) female .The studied students were chosen randomly from 3 secondary schools in EL-Zarka district. 118 students (59.0%) were from rural areas and 82(41.0%) from urban areas.

Exclusion criteria:

Students who did not complete the three doses of HBV vaccine; students with history suggesting clinical evidence of symptomatic HBV infection; students with HBcAbs positive; and subjects with chronic debilitating illness e.g.,: chronic renal failure, malignancy, immunosuppressive therapy were excluded from the study.

All included children were subjected to complete history taking by the self-administered questionnaire, clinical examinations, and laboratory investigations (CBC, Anti HBs antibodies by ELISA and Anti HBc antibodies by ELISA).

Laboratory investigations were done in Damietta University hospital. About 5 mL of venous blood were collected from each subject and divided in tubes prepared for each test. The sera were rapidly removed from the cells after clotting and centrifugation and stored in labeled sterile Ependorff tubes to avoid repeated freezing and thawing. Serum samples for testing for HBV markers were stored frozen at -20 c° before being analyzed in batches, while those for complete blood count were immediately transported to the laboratory for assay. All the serum samples had code numbers and were tested blind. Complete blood count was done using automated analyzer**.** Viral serological markers of HBV were done using ELISA technique. Serum samples were tested for the qualitative and quantitative determination of the anti-HBs, qualitative determination of anti-HBc using commercially available **(Monalisa, France)** kites via the fully automated **(State Fax, Germany),** in accordance with the manufacturer's instructions, levels of anti-HBs were expressed in international units per liter (IU/L). Subjects with non-measurable (0.0) anti-HBs titers were considered non-responders and those with anti-HBs levels < 10 IU/L were considered to be sero - negative. These last two groups were not sero-protected. Those with anti-HBs levels ≥ 10 IU/L. those with anti HBs levels between 10 IU/L and 100 IU/L were rated as having a low immune response and those with anti-HBs levels > 100 IU/L were rated as having a good immune response to the HB vaccine. HBV infections were diagnosed when tests for anti-HBc showed positive results **(EL-Sawy and Mohamed, 2000).) and (Amini *et al.*, 2004**

Data entry and Analysis: The collected data were organized, tabulated and statistically analyzed, using Statistical Package for Social Science (SPSS) version 19 (SPSS Inc, Chicago, USA), running on IBM compatible computer with Microsoft ® Windows 7 Operating System. Mean, standard deviation, range, frequency and percentage were used as descriptive, Fisher exact tests was used for testing significance of observed differences between studied patients. The level of significance was adopted at $p < 0.05\%$.

3. Results

As all our students were negative to HBcAbs , we excluded their infection, and measurement of HBsAb is expression of immunity to HBV vaccine after 15-17 years of 3 doses of HBV neonatal vaccination we found that the titer of HBsAb in 40% of studied students is less than (10 u IU/L) meaning loss of immunity to hepatitis B which increase the need for a booster dose at this age to prevent the break through infection, and 59.5% of waning immunity (HBsAb titer =10-100), compared to only 0.5% with good immunity (table 1). In the present study, there was significant difference between different HBsAb levels as regard to gender distribution (i.e., gender had an effect on seroconversion of HBV vaccine). On the other hand, there was no effect of residence, socioeconomic status, BMI, ICU admission, feeding pattern, Hgb level and WBCs count on the seroconversion of HBV vaccine level (table 2).

Table (1): Distribution of studied cases regarding to HBs Abs

HBs Abs	No =200	%
<10	80	40
10-100	119	59.5
>100	1	0.5
Total	200	100

Table (2): Comparison between different HBsAbs regarding to different variables

	HBsAbs			test	*P*
	<10	**10-100**	**>100**		
Gender					
Male	29(28.2%)	74(71.8%)	0(0.0%)	13.89	<0.001*
Female	51(52.6%)	45(46.4%)	1(0.9%)		
Residence					
Rural	44(37.3%)	73(61.9%)	1(0.8%)	1.44	0.55
Urban	36(43.9%)	46(56.1%)	0(0.0%)		
Socioeconomic level					
Low	15(18.8%)	18(15.1%)	0(0.0%)		
Moderate	58(72.5%)	86(72.3%)	1(0.9%)	2.33	0.7(NS)
High	7(8.8%)	15(12.6%)	0(0.0%)		
BMI centile					
≤ 95 percentile	42(28.0%)	107(71.3%)	1(0.7%)	2.16	0.78(NS)
> 95 percentile	38(76.0%)	12(24.0%)	0(0.0%)		
NICU admission	5(6.25%)	0(0.0%)	0(0.0%)	4.90	0.40(NS)
Feeding					
Breast feeding	62(77.5%)	99(83.2%)	1(100.0%)	1.49	0.50(NS)
Artificial	18(22.5%)	20(16.8%)	0(0.0%)		
Hemoglobin %					
Anemia	11(13.8%)	26(21.8%)	1(100.0%)	2.50	0.30(NS)
Non anemic	69(86.3%)	93(78.2%)	0(0.0%)		
WBCs					
Normal	75(93.8%)	116(97.5%)	1(100.0%)	3.23	0.30(NS)
High	5(6.3%)	3(2.5%)	0 (0.0%)		

4. Discussion

The hepatitis B virus (HBV) is an important agent of hepatitis, cirrhosis and hepatocellular carcinoma in all over the world. Also this infection has been responsible for about 1 million deaths each year **(Batista *et al.*, 2006).** It is estimated that 3% of all people of the world are infected to the virus based on WHO reports **(Fisman *et al.*, 2002).** Immunization is the most effective way to prevent transmission of hepatitis B virus (HBV) and, hence, the development of acute and chronic hepatitis B (**Yu *et al.*, 2004**). Hepatitis B vaccines are highly effective and safe and have been incorporated into national immunization programs in over 150 countries. Fortunately, Egypt is one of these countries. The major humoral immune response is to common determinant of the surface antigen protein of the virus. Approximately 5-10% of healthy immunocompetent subjects do not mount an antibody response (anti-HBs) (**Zuckerman, 2006).** The immunogenicity, efficiency, and safety profile of hepatitis B vaccine has been well established in many previous controlled studies **(Cassidy, 2005)**. It has been demonstrated that 90-99%of healthy neonates, children, adolescents and adults developed protective levels of anti-HBs antibody following a standard vaccination course with hepatitis B vaccine **(Jafarzadeh and Shokri, 2003).** However, with the increasing number of women vaccinated against HBV worldwide **(WHO, 2008)** and the possible role of anti-HBs titer peak on long-term persistence of anti-HBs protector titers further studies will be needed to evaluate the immune response to different vaccine schemes, including different concentrations of recombinant HBsAg **(Bialek *et al.*, 2008).**

Previous studies in Egypt found that the rate of HBsAg positivity among vaccinated children was 0. 8% compared to 2. 2% among the non-vaccinated children (**Reda *et al.*, 2003**). But in our study all students included had no HBcAbs which mean no HBV infection and this reflect the effectiveness of HBV vaccine in prevention of HBV infection. In addition, **El-Sawy and Mohamed (2000)** reported that the prevalence rate of HBV infection in their study population was 0. 56% and HBsAg carrier rate was nil.

The present study aimed to assess the long term immunity to HBV vaccine 15-17 years after complete 3 doses of vaccine at infancy. The overall seroprotection 15-17 years after immunization was 59.5% (HBsAbs 10-100IU/l) and only 0.5% of the children had titers > 100 IU/L. Compared to other studies performed with extension of the age range up to 15 years, **Ni *et al.* (2004)** reported that, HBsAb seropositivity levels among 75.8% and 79% of their subjects respectively.

In the present study the percentage of non-

protective HBsAb levels is 40%, while, **Ni *et al.* (2001)** have reported values of 60.7% with non-protective HBsAb levels**.** The low level of HBsAb reported in the present study and the diversity of results in the different studies can be attributed to several factors: ***First***, the type of vaccine, whether it is a plasma-derived or yeast-derived vaccine could play a role. **Da Villa *et al.* (2006)** found that the DNA recombinant vaccine gave a higher titer (97.6%) than the plasma-derived vaccine (80.4%), while **Floreani *et al.* (2006)** recorded a slightly higher titer with plasma-derived vaccine than with yeast-derived vaccine (87.8% and 81.6% respectively). ***Second***, the schedule of immunization may also play a role in determining HBsAb level. **Da Villa *et al.* (2007)** found that a higher level of protective HBsAb was achieved when the vaccine doses were administered after the third month of life rather than in the first 3 months, while **Williams *et al.* (2007)** found that persistence of protective levels for a longer period occurred when the vaccine doses were administered soon after birth. ***The Third factor*** is the dose of the vaccine (**El-Sawy and Mohamed, 2000).**

In the present study, there is significant difference in the frequency of HB vaccine seroprotection between males and females. Seroprotection rate and titer of anti-HBs were higher in males than females; there was less number of boys with anti-HBs< 10 mIU/ml (28.2% of males vs 52.5% of females). This may explained by the effect of gender on level of seroprotection, This is in agreement with some studies, **(Lin, 2005)**; while others have found that male sex is a predictor of non-response (**YU *et al.*, 2008)**.

Hagedorn (2010) reported that the predictors of non-protective levels of HBsAb were: increasing age, male gender and obesity**,** but other studies show no significant difference in the frequency of HB seroprotection between males and females **(Middleman *et al.*, 2007). Behairy *et al.* (2009)** detected that males may retain anti-HBsAb titers of higher values than females. There was statistically significant difference in levels of HBsAb between boys and girls.

In the present work, there was no significant effect of BMI on seroprotection of HBV vaccine. These results are comparable to with **Keating *et al.* (2003),** as they reported that the greater the body mass index the less the immune response, but with no significant difference, while **Charles *et al.* (2005)** showed that the advancing age, obesity and smoking in adults have negative influence on the efficacy on hepatitis B vaccination and explained that effect by the deposition of the vaccine in fat rather than in muscle resulting in higher failure rates.

It has been shown that the immunity rates after vaccination in obese subjects are lower than the controls and the exact mechanism is not clear **(Mandell *et al.*, 2005).**

In the present study the majority of students included (72%) are of moderate socioeconomic standard, although the seroprotection level of HBsAbs level increased gradually with increased socioeconomic standard, there was no difference between those of high and low standard as regard HBsAbs level. Some investigators correlate the socioeconomic state with vaccine response (**Charles *et al.*, 2005)**.

Wang *et al.* (2006) reported that universal hepatitis B vaccination program (UHBVP) was less effective in socio-economically disadvantaged area and the long-term efficacy and immunogenicity of vaccination were modified by host factors and factors associated with urbanization. They

In the present study, only 0.5% of studied students had long term immunity to hepatitis B vaccination after a period extended to more than 15 years, a booster dose of HBV vaccine is recommended after this age. This agrees with **Jan (2010)** as he found that at least one-quarter of HB vaccines have lost their immune memory to the HB vaccine when entering college. Immune memory to HB vaccine was identified by early seroconversion, which was present in only 20% of vaccines in his study. To ensure higher than 90% anti-HBs seroconversion rates, at least 2 doses of HB booster vaccines are recommended for at risk youths who received complete HB vaccinations in neonatal or infant periods but are seronegative for HBsAg, anti-HBs, and anti-HBc in adolescence**.**

On contrary, **Dentinger *et al.* (2009)** reported that up to age 16 years, booster doses of HB vaccine are not required to protect against clinically significant disease. In a long study for 18 years, **Yuen *et al.* (2008)** stated that the long-term immunogenicity and efficacy of hepatitis B virus (HBV) vaccination remain to be defined. They aimed to examine the long-term immunogenicity and efficacy of HBV vaccination over 18 years of follow-up and concluded that because of the highly effective anamnestic responses, a booster dose was not necessary at least up to 18 years after the primary vaccination. Other investigators still raise the possibility for a booster dose, **Wang *et al.* (2010)** cleared that their previous study suggests that routine booster vaccination may not be necessary to provide protection against chronic HBV infection before age 15 years, as the maintenance of HBsAg-specific memory confers protection against a clinical break-through infection even in the absence of detectable antibodies. However, the possibility of a need for a

booster dose exists, particularly when the child becomes adolescent. Whether primary HBV vaccination in infancy can provide protection in adolescence remains to be elucidated.

In short, results of the present study revealed that, although 40% the studied children had non-protective levels of HBsAb and this puts them at risk of infection, HBV vaccine is protective against HBV infection as none of vaccinated students showed clinical evidence of symptomatic hepatitis and they were all negative to HBcAbs. No effect of urbanization, socioeconomic standards, BMI or Hgb% on level of HBsAb seroprotection. Hepatitis B vaccine has long lasting immunity extended to at least 15 years.

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