Effectiveness of Hepatitis B vaccination in children of chronic hepatitis B mothers

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ABSTRACT

Objective: Although all newborns in Iran have been vaccinated against hepatitis B since March 1993, routine screening of pregnant women has not been conducted in prenatal care programs, yet transmission of hepatitis B via the maternal-fetal route is still a viable likelihood, which must be entertained.

Methods: The subjects were divided into 2 groups. The exposed group comprised 97 vaccinated children whose mothers were seropositive for hepatitis B surface antigen (HBsAg) and had not received hepatitis immunoglobulin at birth. The unexposed group consisted of 87 vaccinated children whose mothers were seronegative for hepatitis B surface antigen. We compared these 2 groups to determine the efficacy of vaccine alone in high-risk children. This study was conducted in Tehran, Iran, from June 2002 to December 2002. All children were born after 1993.

Results: Chronic infection (HBsAg positivity) was detected in 14.3% of children in the exposed group. There were no instances of chronic infection in the unexposed group (relative risk [RR]=13.48, 95% confidence intervals [CI] 1.8-100.02). Previous infection of hepatitis B (HBcAb positivity) was found in 29 (29.9%) children in the exposed group, but only one (1.2%) in the unexposed group (RR=26.01, 95% CI: 3.61-186.95). Immunity (HBsAb positivity) in the exposed group measured 48 (49.5%) and unexposed group measured 56 (64.4%) (R.R=0.76, 95% CI: 0.59-0.99).

Conclusion: Vaccination alone did not induce immunity against hepatitis B in high-risk children; it seems that routine screening of pregnant women is necessary for determining whether neonates need hepatitis B immunoglobulin after birth.

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Over 2 billion people worldwide have been exposed to hepatitis B virus (HBV) and 350 million are chronic carriers of HBV.[1,2] While over 35% of Iranians have been exposed to HBV, approximately 2% are chronic carriers and HBV is the most frequent cause of end stage liver disease in this country.[3] Hepatitis B vaccine is highly immunogenic and effective in preventing infection among children and adults, with an overall efficacy of 80-95%.[4-6] Hepatitis B vaccination strategies may vary from one country to another, depending on HBV endemicity, predominant modes of the infection, age of contracting the infection, and available health care resources.[7] Protective efficacy following complete vaccination exceeds 95%.[8,9] In some countries, high protective efficacy rates have been reported without concomitant administration of hepatitis B immunoglobulin (HBIg) to high risk

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infants whose mothers were hepatitis B surface antigen (HBsAg) positive.[10-12] Besides, the results of some studies in Taiwan and Hong Kong showed that the protective efficacy of vaccine alone was significantly low, especially when the mother is hepatitis e antigen (HBeAg) positive.[13,14]

Hepatitis B vaccination has become a part of the Expanded Program for Immunization in Iran since March 2003 and all newborns have been covered by the program and have received the vaccine according to a 3-dose course: the first dose at birth, the second dose at 1.5 months after birth, and the third dose at ninth month after birth.[15] Screening of pregnant women for hepatitis markers was not carried out routinely in prenatal care programs in Iran yet, therefore many of the high-risk infants have not received any passive immunization after birth. This study was designed to determine the efficacy of vaccination alone in high-risk children born after March1993 in Iran.

Methods. This study was performed in 2 gastrointestinal clinics in Tehran (the capital of Iran) during the year 2002. We collected medical data from 97 HBsAg positive mothers whose children were in the exposed group and were born after 1993. The mothers were known cases of hepatitis B before enrollment in the study and their first child bearing that were referred to hepatitis clinics for routine medical visits. All medical records of families were reviewed and the mothers' stage of disease (carrier, chronic hepatitis or cirrhosis) was determined. There were 87 HBsAg negative mothers whose children were in the control group and were born after 1993. Both case and control group samples were selected from a same residential area; socially, medically and economically deprived cases were not under care of our centers. The first children of case group mothers were included in this study if they had the history of vaccination according to the modified national vaccination program (0, 1.5, 9 months). Exclusion criteria were hemophilia, surgery, tattooing, hemodialysis, having received blood products, having received hepatitis B immunoglobulin at birth, and HBsAg positivity in fathers (HBV infection status in other members was not checked routinely in the study). In this study, chronic infection was inferred by the presence of HBsAg, previous exposure to hepatitis B was inferred by the presence of hepatitis B core antibody (HBcAb), and immunity against hepatitis B was inferred by the presence of hepatitis B antibody (HBsAb). Immunity by vaccination is achieved whenever HBsAg is negative, HBsAb is positive and HBcAb is negative. All clinical tests were based on the results of a single blood specimen. A chronic hepatitis B patient was defined as a) having positive HBsAg and an alanine transaminase (ALT) level twice the upper limit of the normal range value after excluding other known etiologies, with or without confirming biopsy results, or b) having positive HBsAg and an ALT level between 1.5-2 times greater than the normal range, and Knodell's histology activity index of 4 or more in liver biopsy. A hepatic cirrhosis patient was defined based on ultrasonographic findings (splenomegaly and ascites) with either of the following criteria: a) presence of esophageal varicose (in upper gastrointestinal endoscopy), b) presence of platelet count <80000/micL, c) prothrombin time more than 3 seconds above normal limit or the presence of cirrhotic findings in liver biopsy alone.

All families were informed regarding the study objectives, and were asked to participate in the protocol. The care-providing physician informed the mothers of their test results. Hepatitis B surface antigen, HBsAb, HBeAg, hepatitis B e antibody (HBeAb), HBcAb, levels of ALT and aspartate transaminase (AST) that were checked in exposed group mothers at the time of diagnosis of the disease in them and was filed in their medical records were included. Hepatitis B surface antigen, HBsAb, and HBcAb were checked in their children (exposed and unexposed group). Hepatitis B surface antigen and HBsAb were checked in mothers of children in unexposed group. The childrens' fathers were also tested for HBsAg. All tests were carried out with a commercial enzyme-linked immunosorbent assay (ELISA) kit (Sorin Biomedica, Italy). Windows®-based SPSS software version 11 was used for statistical analysis of the relative risk. In cases where the value of a cell in one of the tables was zero, 0.5 was added to the cell value. Quantitative variables had a normal distribution (shown by Kolmogorov-Smirnov test). Mann-Whitney U test was used to compare the 2 groups when $p>0.05$. The association between qualitative variables was analyzed using chi-square test. *P* value was calculated with the Monte Carlo test. When $p<0.05$, the association was considered as significant.

Results. Mean ± SD age of children in the exposed group was 6.3±1.9 years and in the unexposed group was 6.5± 1.9 years. The comparison of the prevalence of HBsAg, HBsAb, and HBcAb of children in exposed and unexposed groups was summarized in **Table 1**. Efficiency of vaccination in children in both groups was associated with a relative risk (RR) of 0.58, and 95% confidence interval (CI) measured 0.43-0.79. This means that children with seronegative HBsAg mothers were twice as immune against hepatitis B as children with seropositive HBsAg mothers. Within mothers of children in this group 83 (85%) were carriers, 12 (13%) had chronic hepatitis, and 2 (2.2%) had cirrhosis. No significant association was

Table 1 - Prevalence of hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb), and hepatitis B core antibody (HBcAb) in exposed and unexposed groups.

Serologic markers	Unexposed* (N=87)		Total n (%)	Exposed† (N=97)		Total n (%)	RR	95% CI
	Positive n (%)	Negative n (%)		Positive n (%)	Negative n (%)			
HBsAg	0	87 (100)	**87 (100)**	14 (14.3)	83 (85.7)	**97 (100)**	13.48	1.8 - 100.02
HBsAb	54 (64.4)	31 (35.6)	**87 (100)**	48 (49.5)	49 (50.5)	**97 (100)**	0.76	0.59 - 0.99
HBcAb	1 (1.2)	86 (98.9)	**87 (100)**	29 (29.9)	68 (70.1)	**97 (100)**	26.01	3.61 - 186.95

*Children with seronegative HBsAg mother, †Children with seropositive HBsAg mother, RR - relative risk, CI - confidence interval

Table 2 - Comparison between alanine transaminase (ALT) and aspartate transaminase (AST) levels in mothers of children in the exposed group and their children's virologic seromarkers.

Serologic markers	ALT			AST		
	Median	Mean ± SD	*p* value*	Median	Mean ± SD	*p* value*
HBsAg						
Positive	25	40.3 ± 34.1	0.04	24	37.3 ± 38.7	0.53
Negative	20	31.5 ± 42.1		25	31.8 ± 27.2	
HBsAb						
Positive	20	29 ± 23.5	0.59	24	31.9 ± 28.9	0.76
Negative	21	36.9 ± 54.1		25	33.3 ± 29	
HBcAb						
Positive	21	32.1 ± 27.1	0.59	24	31.2 ± 27.7	0.71
Negative	20	33.1 ± 46		25	33.1 ± 29.5	

*based on Mann-Whitney U test

found between the mother's diseases stage and the children's HBsAg status (x^2=1.8, df=2, p=0.53). There were no significant associations between mother's disease stage and children's HbsAb status (x^2=0.06, df=2, p=1), or children's HBcAb status (x^2=2.1,df=2, p=0.3). The mean and SD of ALT in mothers of children in the exposed group measured 22.8± 41 and AST 32.6± 28.8. **Table 2** shows the association between ALT and AST levels in mothers of children in the exposed group and their children's virologic seromarkers. Twenty-three (36.5%) mothers' of children in the exposed group were HBeAg positive and 40 (63.5%) were HBeAg negative; 41 (64.1%) of them were HBeAb positive and 23 (35.9%) were HBeAb negative. Within HBeAg positive mothers HBsAg was found in 34.8% of children whereas this proportion was 2.5% in children of HBeAg negative mothers; there was a significant association between HBeAg status of mothers and HBsAg status of children (RR=13.91, Fisher exact test was 0.001). Hepatitis B e antibody of these mothers also had a significant association with HBsAg of their children (RR=0.007, Fisher exact test: 0.001).

Discussion. The main finding of this study was that hepatitis B vaccine is devoid of sufficient efficacy in providing protection against hepatitis B in high-risk children. Markers of HBV infection were detected in approximately 30% of cases and chronic carrier rate was measured at 14.4%; however, in other studies the efficacy of HBV vaccine in high-risk children was shown to be higher than in the present study. In Sweden, 212 children whose mothers were carriers of hepatitis B were followed up for 2-9 years after birth. A combination of passive and active immunization schedule (HBIg and HBV) was used in children of HBeAg-positive mothers. Of 25 children of such

mothers, one was HBsAg carrier and 5 had asymptomatic seroconversion. None of 15 newborns with negative HBeAg and HBeAb mothers, just vaccinated against HBV were HBsAg carriers; however, there was one case of asymptomatic seroconversion. Immunization of children with HBeAg-negative/HBeAb-positive mothers was withheld between 1983 and 1987. Of 90 children, only one was HBsAg carrier and 8 were asymptomatic with seroconversion.[16] In another study performed in China, 171 infants of positive HBeAg mothers were followed up until 5 years after birth. The infants were divided into groups A, B and C. Group A (53) and group B (57) received 4 doses of hepatitis B vaccine (20 mg doses in group A and 10 mg doses in group B) at birth, and 1, 2, and 12 months after birth. Group C (61) received 3 of 20 mg doses of hepatitis B vaccine at birth, and 1 and 6 months after birth. Natural infections (persistence or reappearance of hepatitis B core antibody) occurred in only 12% and none of them became HBsAg positive.[17] Given the low rate of infection in the unexposed group, maternal transmission is the most probable route of childhood infection in the exposed group; however, it may occur as horizontal transmission. Moreover, the probability of horizontal childhood transmission within the community is clearly less than the one in the unexposed group. While the source of previous infection is a matter of question in the exposed group, lack of any chronic infections and only one case of previous infection in the unexposed group, indicate the absence of horizontal transmission in vaccinated children. We can assume that routine neonatal vaccination has effectively stopped transmission in the unexposed group. Since the main route of transmission in this group (especially in the age group studied) is horizontal, efficacy of the vaccine was evident. Previous investigations in the Iranian population, which have compared the efficacy of hepatitis B vaccine before and after the implementation of Expanded Program of Immunization (EPI) bear out our results. Another study carried out in Iran showed a significant reduction in the rate of HBsAg positivity in the subgroup of children aged 2-14 years (1.3% versus 8%, $p<0.05$) after EPI.[18] The comparison showed a significant decrease in the prevalence of hepatitis B in vaccinated neonates; this is similar to findings of reports from other parts of the world.[14] Kohn et al[19] observed high-risk children 18-months after complete vaccination in 1996. Of 426 cases studied, 269 (63%) had been completely vaccinated. One hundred and ninety-four children (46%) had been tested for hepatitis B surface antibody (anti-HBs) and 163 (38%) had been tested for HBsAg. Six children tested (4%) were HBsAg-positive and 22 (11%) were anti-HBs negative. They suggested that the program had prevented both HBV infection (74%) and HBV carriage (87%) in high-risk children.[19] The effect of HBV vaccine on maternal-fetal transmission is also of great significance. For instance, the possibility of chronicity is higher if transmission occurs during infancy;[20,21] but it is strongly related to HBeAg and HBeAb status of the mother. It has been shown that chronicity will occur in the infants of 85-90% of HBeAg positive and 32% of HBeAg negative mothers.[22] Our results demonstrated this relationship in the exposed group. Recent data on Iranian patients showed that over 60% of the HBsAg positive population in Iran was HBeAg negative.[23,24] This was confirmed by our results. If we calculate the possibility of chronic infantile infection with such a ratio of HBeAg positivity, the possibility of chronicity in the exposed children will be more than 40%. Hence, neonatal vaccination stopped the development of hepatitis B in almost 25% of the children in the exposed group (a relative risk reduction of approximately 60%). However, vaccination stopped transmission in the high-risk group partly, rather than completely. Recent data from a national Iranian health survey yielded the same finding by comparing vaccinated and non-vaccinated children of chronic carriers; although the difference was not significant.[25] Interestingly, the immunity ratio in the vaccinated group did not exceed 50% in exposed children, and 65% in the unexposed children. Whether negative HBsAb in these vaccinated children translates into lack of immunity, is a matter of discussion, and it seems that in the low-risk general population, the latency of serum HBsAb reduction does not correlate with the non-immune state.[26-30] This is related to the role of memory immune cells after initial exposure to the antigen.[31] It should be emphasized that the children studied in the latter investigation were aged over one year, a time when antibody levels may decline spontaneously.[32] Studies on the Iranian population during childhood and early teenage have also yielded similar negative HBsAb ratios.[33]

This study provides preliminary data in support of the view that the protocol currently enforced in countries such as Iran, prescribing hepatitis vaccine alone for high-risk children, is inadequate. Although no arguments can be made against the continuation of routine neonatal vaccinations, the urgency of enforcing routine maternal screenings must be stressed. It must be noted that existing data only show the epidemiological aspect of the problem. Thus, contriving a nationally accepted plan requires further analysis with attention to the efficacy of passive immunization, cost of prevention, the use of prenatal maternal screening, and costs of care for hepatitis B patients.

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