Short communication

Serum level of anti-hepatitis B surface antigen 6–8 years after hepatitis B vaccination at birth

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المستويات المصلية للمستضد السطحي للالتهاب الكبدي B بعد 6 – 8 سنوات من تلقي لقاح الالتهاب الكبدي B وقت الولادة

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الخلاصة: نظراً لعدم معرفة مدة الحماية التالية للتلقيح ضد الالتهاب الكبدي B للأطفال؛ صمَّم الباحثون هذه الدراسة للتعرف على مستوى أضداد ومستضدات الالتهاب الكبدي السطحية في المصل لدى 273 من أطفال مدارس مدينة زنجان، بجمهورية إيران الإسلامية، ممن تتراوح أعمارهم بين 7 و9 سنوات؛ والذين تلقّوا لقاح الالتهاب الكبدي B عند ولادتهم. مع اعتبار العيارات التي تساوي أو تقل عن 10 مكرو وحدة/مل غير واقية. وقد لوحظ أن ما يزيد على نصف الأطفال الخاضعين للدراسة (52 %) لديهم عيار مساوٍ أو أقل من ذلك، دون تفريق بين الجنسين، في حين كان المستضد السطحي للالتهاب الكبدي B غير موجود لدى 81 طفلاً (29.1 %). وكان لدى 3 أطفال أضداد للبروتين اللبي للالتهاب الكبدي B. وتمس الحاجة إلى مزيد من الدراسات للتعرف على ضرورة إعطاء الجرعات المعزِّزة الضرورية وتوقيتها.

ABSTRACT The duration of protection after hepatitis B vaccination in children is unknown. We determined the serum level of antibody to hepatitis B surface antigen (anti-HBsAg) in 273 randomly selected 7–9-year-old schoolchildren from Zanjan City, Islamic Republic of Iran, who had been fully vaccinated against hepatitis B starting at birth. Titres ≤ 10 mIU/mL were considered unprotective. Just over half of the children (52%) had titres ≤ 10 mIU/mL with no difference between the sexes, while 81 (29.7%) had no anti-HBsAg (0 mIU/mL). Three of the children had antibodies to hepatitis B core protein. More studies are needed to determine the necessity for or timing of booster doses.

Concentration sérique en anticorps antigène de surface de l'hépatite B 6 à 8 ans après la vaccination contre l'hépatite B à la naissance

RÉSUMÉ La durée de la protection après la vaccination des enfants contre l'hépatite B est inconnue. Nous avons déterminé le taux sérique d'anticorps dirigés contre l'antigène de surface du virus de l'hépatite B (anti-HBs) chez 273 écoliers âgés de 7 à 9 ans de la ville de Zanjan (République islamique d'Iran) choisis au hasard, qui avaient bénéficié d'une vaccination complète contre l'hépatite B dès la naissance. Des titres inférieurs ou égaux à 10 mUI/mL étaient considérés comme non protecteurs. Pour à peine plus de la moitié des enfants (52 %), les titres étaient inférieurs ou égaux à 10 mUI/mL, quel que soit le sexe, alors que 81 d'entre eux (29,7 %) n'avaient pas d'anticorps anti-HBs (0 mUI/mL). Trois enfants présentaient des anticorps dirigés contre l'antigène central du virus de l'hépatite B (anti-HBc). D'autres études sont nécessaires pour établir la nécessité de doses de rappel ou leur calendrier d'administration.

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Introduction

Hepatitis B virus (HBV) is a major global health concern with >350 million people chronically infected [*1*]. The prevalence of hepatitis B carriers varies in different parts of the world, ranging from less than 1% to 15% [*2*]. A large number of cases are seen in eastern Asia and sub-Saharan Africa [*3*]. It is estimated that over 35% of Iranians have been exposed to HBV and about 3% are chronic carriers, ranging from 1.7% in Fars Province to over 5% in Sistan va Balouchestan [*2*]. It appears that 8% of Iranians infected with HBV will become chronic carriers [*2*]. In 1991, the World Health Organization (WHO) recommended that hepatitis B vaccination be included in national immunization programmes in countries with a hepatitis B surface antigen (HBsAg) carrier prevalence of 8% or greater by 1995 and in all countries by 1997 [*4*]. The strategy for the control of HBV infection, as outlined by the WHO and endorsed by the Advisory Committee on Immunization Practices (ACIP), is the introduction of hepatitis B immunization at birth [*5,6*]. This strategy has dramatically reduced the carrier rate of HBV and significantly decreased the incidence of childhood hepatocellular carcinoma in many areas of the world [*7*]. It has been reported that when hepatitis B vaccination is initiated at birth, there is an increased likelihood that the child will complete the series [*8,9*] hence an advantage of starting immunizing at this point. The neonatal vaccination programme for hepatitis B was launched in 1992 in the Islamic Republic of Iran.

The duration of hepatitis B vaccine protection has not been firmly established [*10*]. Zanetti et al. suggested that strong immunological memory persists more than 10 years after immunization of infants and adolescents with a primary course of vaccination, and a booster dose does not seem necessary [*11*]. McMahon and colleagues reported that hepatitis B vaccination strongly protects against infection for at least 15 years, that antibody levels decrease the most among persons immunized at 4 years of age or younger, and that a booster dose is not needed before the onset of sexual activity [*12*].

In the Islamic Republic of Iran the level of antibodies to hepatitis B in vaccinated individuals is not known. Therefore, we examined the long-term persistence of antibody to HBsAg (anti-HBsAg) in 7–9-year-old children who had been vaccinated at least 6–8 years before with 3 doses of hepatitis B vaccine starting at birth to provide information on the effect of the immunization strategy for hepatitis B and the need for booster doses.

Methods

This was a cross-sectional serological study carried out from February 2003 to February 2004 in Zanjan City. Zanjan City is in the centre of Zanjan province, north-west Islamic Republic of Iran, and has 1 million inhabitants (1.5% of the Iranian population).The distribution of health care services is good throughout the territory, and vaccinations are delivered through local health districts which are able to reach the whole population.

The sample consisted of 300, 7–9-year-old schoolchildren. The minimum sample size for the study was calculated as 273, assuming 23% of children had non-protective serum level of anti-HBsAg [*10*], with 95% confidence interval and 5% error. The children were drawn from 30 (out of 187) randomly selected primary schools in the city; 10 children were selected from each school by systematic random

sampling. Only children who received all 3 doses of hepatitis B vaccine after birth were included in the study. This was ascertained by vaccination certificates recorded at the Public Health Service or at the local health units which were consulted for each year of the study and matched with birth certificate data. In our country, hepatitis B vaccination is initiated within the first 7 days of life, with the second dose given at 8 weeks and the third at 12 months of age.

The purpose and potential risk factors of this study were explained to all the subjects and their parents before informed consent was obtained. The study procedures were approved by an institutional review board of Zanjan University of Medical Sciences.

The accepted protective concentration of serum anti-HBsAg was considered > 10 mIU/mL [*10*]. A 5-mL blood sample was collected from each child and the serum level of anti-HBsAg was measured. We also assessed antibodies to HBV core protein (anti-HBc) in all serums to check for hepatitis B infection.

Antibody testing was performed at Vali-Asr laboratory, using a commercial HBsAb and HBcAb ELISA system (Radium, Italy) and following manufacturer's instructions. For privacy reasons, sera were anonymous to laboratory personnel; the only identifying data being age and sex. Demographic factors (other than sex and age) were not considered in the current study. For descriptive analysis results are shown as absolute numbers and percentage. *SPSS*, version 10 was used for analysis.

Results

A total of 300 children 7–9 years of age were selected. The final sample consisted of 273 children [134 boys (49%) and 139 girls (51%)] because the parents of 27 children did not agree to participate in the study. The children were divided into 3 groups according to age: 7 years group (89 children, 32.6%), 2) 8 years group (88 children, 32.2%), and 3) 9 years group (96 children, 35.2%).

Table 1 **Serum levels of anti-hepatitis B surface antigen (HBsAg)**

Anti-HBsAg serum levels (mIU/mL)	No. (*n* = 273)	%
0	81	29.7
0–10	61	22.3
10–100	75	27.5
> 100	56	20.5

Table 2 **Number of hyporesponders to hepatitis B vaccination (anti-hepatitis B surface antigen levels ≥ 10 mIU/mL) according to age**

Age of children (years)	No. (*n* = 142)	%
7	45	31.7
8	45	31.7
9	52	36.6

Table 1 shows the anti-HBsAg levels in the serum of the studied children. Table 2 illustrates the frequency of hyporesponders to hepatitis B vaccination according to age. There were no significant differences by sex and age. Our study showed that 52.0% of the children had low serum titre of anti-HBsAg (≤ 10 mIU/mL), and more than half of these (29.7% of the total) had no serum titre of anti-HBsAg (0 mIU/mL). Thus at the 95% confidence interval level, serum levels of anti-HBsAg were non-protective in 46%–58% of school-aged children of Zanjan. In effect, half of vaccinated children were non-responders to hepatitis B vaccine or had a rapid fall-off of anti-HBsAg levels in

Zanjan according the results of our study.

We also found that 3 children (1% of total) (1 boy, 2 girls) had positive anti-HBc in their serum; 2 of them were also hyporesponsive for anti-HBsAg.

Discussion

In the current report, we studied groups of children aged 7–9 years who had been vaccinated with 3 doses of a hepatitis B vaccine in infancy and showed that 52% of them had low serum titre of anti-HBsAg (≤ 10 mIU/mL), and more than half of these (29.7% of the total) had zero serum titres. There were no differences between boys and girls.

Our findings of the loss of anti-HBsAg over time differ from those reported by other researchers. A study of children at 12 years of age who had received a plasma-derived vaccine in infancy and were at low risk for hepatitis B exposure found that none had anti-HBsAg < 10 mIU/mL [*10*]. Another study followed children at low risk who were vaccinated in infancy with a recombinant vaccine [*10*]. By 5 years of age, only 7% had titres of anti-HBsAg < 10 mIU/mL. The major difference between the children in those studies and ours is their age at initial vaccination. Those subjects were 2–3 months of age or older when they began their hepatitis B vaccination, whereas the children in our study began their series in the first week of life, a schedule recommended by ACIP. Some studies suggest that starting the initial vaccination series later in infancy may result in better persistence of anti-HBsAg as the prevalence of anti-HBsAg titres ≥ 10 mIU/mL ranged from 79% to 85% at 10–12 years of age [*13,14*]. In another study of 1630 persons, anti-HBsAg titres were >10 mIU/mL in 76% of the sample 10 years after vaccination and in 82% of those age 6 months–19 years at the time of vaccination [*10*].

Symptomatic hepatitis B is very rare in immunized persons who have antibody titres ≥ 10 mIU/mL, although there is eventual loss of detectable antibody in up to 50% of these persons 5 to 10 years after immunization [*15*]. The latter idea concurs with our results. Some may have anti-HBc that are indicative of HBV infection, but there is usually no evidence of disease [*15*]. In our research 1% of the children had positive results for anti-HBc.

A study from Hawaii of low-risk infants given recombinant vaccine starting at birth showed that only 19% had anti-HBs > l0 mIU/mL at 6 years, yet all responded to a booster dose [*16*]. Booster doses of hepatitis B vaccine are not currently recommended [*10,16*]. It would seem that they are not needed before the onset of sexual activity and the long-term effectiveness of hepatitis B vaccine, even in those who have lost detectable anti-HBs, militates against routine monitoring of anti-HBs titres and the administration of late booster doses [*15*]. Our study showed that vaccine efficacy against infection waned with time, 48% of the children had antibody level greater than 10 mIU/mL and 22.5% had measurable antibody levels, which is considered sufficient to prevent infection, so a booster dose is not recommended for these 2 groups. However, about 29.7% had no antibody at all. A larger study is necessary before we can conclude that a booster dose is needed for this group of children but we think a booster dose may be needed for children who have undetectable antibody after at least 5 years of universal hepatitis B vaccination. However, some believe that in populations at high risk for continuing exposure to hepatitis B virus, hepatitis B vaccine is protective for at least 10 years, the time during which the greatest risk of

chronic infection after exposure occurs [*17*]. Some data suggest that one-fourth of children who responded to a plasma-derived hepatitis B vaccine in infancy lost protective antibody by early adolescence and did not show evidence of an anamnestic response to a booster dose, although the small number of participants makes it difficult to draw precise conclusions. In addition, the lack of an anamnestic response may not mean that children are not protected against HBV disease [*10*]. The long-term protection afforded by immunization reflects the normally lengthy incubation period of hepatitis B, which permits previously immunized persons to mount protective anamnestic antibody responses on exposure to virus [*15*].

In conclusion, our results showed that the anti-HBsAg level was < 10 mIU/mL 6–8 years after the last dose of hepatitis B vaccine in nearly half of the children who were vaccinated from birth. Long-term follow-up studies at school entry and at adolescence, including ones evaluating the effects of a booster dose at these times, may be needed to determine the duration of protection and the necessity for or timing of booster doses for low-risk children initially vaccinated for hepatitis B starting at birth. We think a booster dose may be needed for children who have undetectable antibody levels after at least 5 years of universal hepatitis B vaccination.

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Correction

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