The Turkish Journal of Pediatrics 1997: 39: 483-489

INTRADERMAL ADMINISTRATION OF HEPATITIS B VACCINE IN INFANTS AND PRESCHOOL CHILDREN*

*Zafer Kurugöl MD***, *Ayten Egemen MD****, *Selda Erensoy MD*****
*Altınay Bilgiç MD******, *Necil Kütükçüler MD*******

SUMMARY: Kurugöl Z, Egemen A, Erensoy S, Bilgiç A, Kütükçüler N. (Departments of Pediatrics and Microbiology, Ege University Faculty of Medicine, İzmir, Turkey). Intradermal administration of hepatitis B vaccine in infants and preschool children. Turk J Pediatr 1997; 39: 483-489.

One of the ways to administrate hepatitis B vaccination is the intradermal (id) route. The aim of this study is to evaluate the immunologic response of various age groups of children who received three 2 µg id doses of recombinant hepatitis B vaccine. One hundred and eighty-seven children (86 infants, 101 preschool children) were administered a 2 µg dose of recombinant hepatitis B vaccine (Gen Hevac B) intradermally zero, one and six months. Eight weeks after the third vaccination, the gometric mean titers (GMT) of antibody to hepatitis B surface antigen (anti-HBs) of infants was 753 IU/L; that of preschool children was 799 IU/L. There was no statistically significant difference between the anti-HBs GMT of infants and preschool children. However, infants were less likely to have developed protective anti-HBs (≤ 10 IU/L) than preschool children (93% vs 100%, p = 0.009). In 8.1 percent of infants and 3.9 percent of preschool children, local reactions were observed. The 2 µg recombinant vaccine by id route is safe and suitable for immunization of preschool children. The id route is technically difficult to administrate in infants and protective seroconversion rates are lower than in preschool children. *Key words: intradermal hepatitis B vaccine, infant, preschool children.*

Hepatitis B virus (HBV) infection, with its chronic sequelae of cirrhosis of the liver and hepatocellular carcinoma, constitutes a major health problem[1,2]. In areas of high and intermediate endemicity, large-scale immunization programs aimed at mass immunization of all infants, adolescents, and other individuals at high risk should be applied where economically feasible[1]. Turkey has an intermediate endemicity for HBV infection. In Turkey, hepatitis B surface antigen (HBsAg) and the antibody to HBsAg (Anti-HBs) positivity ranges are reported to be 3-15 percent and 26.2-68.8 percent, respectively[3-10]. Vertical transmission is probably not the major mode of transmission in Turkey[8]. HBsAg positivity is more prevalent in children under five years of age, suggesting an early exposure

* From the Departments of Pediatrics and Microbiology, Ege University Faculty of Medicine, İzmir.

** Pediatrician, Ege University Faculty of Medicine.

*** Professor of Pediatrics, Ege University Faculty of Medicine.

**** Associate Professor of Microbiology, Ege University Faculty of Medicine.

***** Professor of Microbiology, Ege University Faculty of Medicine.

****** Associate Professor of Pediatrics, Ege University Faculty of Medicine.

of young children and horizontal transmission in Turkey[4]. Therefore, screening and immunization of babies born to carrier mothers would not be an effective strategy. If the mass vaccination program is not available, immunization of all preschool children in Turkey can prevent horizontally transmitted HBV infection.

One of the ways to apply hepatitis B vaccination is the intradermal (id) route. To date, various studies have been made to evaluate the anti-HBs response in adults after administration of various hepatitis B vaccines by the id route[11-19]. However, there has been only one study that evaluates the response following an id plasma-derived hepatitis B vaccine in infants[20]. no study has been found which assesses the effectiveness of id recombinant hepatitis B vaccine in infants or children.

The aim of this study is to evaluate the immunologic response of various age groups of children who received three 2 µg id doses of recombinant hepatitis B vaccine.

Material and Methods

One hundred and eighty-seven healthy children (97 female, 90 male) were enrolled in this study. Eighty-six were infants of two months of age, and 101 were preschool children between one and six years of age. Infants were full-term and healthy with a mean birth weight of 3375 ± 426 grams. Mothers of infants, infants and preschool children were all negative for HBsAg, anti HBs, and anti-HBc.

A recombinant hepatitis B vaccine containing 20 µg HBsAg per 0.5 ml (Gen Hevac, Pasteur Mériux) was used in this study. In many studies, 2 µg doses of various hepatitis B vaccines were administrated by id route[11-20]. Infants were administered a 2 µg dose id vaccine in the deltoid region at two, three, and eight months of age (0, 1, 6 months scheme). At two and three months of age, all infants also received regularly scheduled doses of diphtheria-tetanus-pertussis (DTP) and oral polio vaccines. Hepatitis B vaccines were administrated in the right arm and the DTP vaccine in the left arm. Preschool children were administered the same dosages of vaccines in the same region, on a schedule similar to that for the infants (at 0, 1, 6 months). During their follow-up in the out-patient clinic of the Social Pediatric Unit, all vaccines were observed for side effects. The parents were informed to record side effects such as local tenderness, erythema, induration, hyperpigmentation, fever, and irritability. If any side effect was to occur they were to bring their children to our clinics. Persistent induration and hyperpigmentation were assessed after a month of each dose.

Postvaccinal blood samples were collected from all infants and preschool children eight weeks after their last vaccination and were tested for anti-HBs levels by microparticle enzyme immunoassay (IMx, Abbott Diagnostics, USA) quantitatively[21].

Immunologic response of the children was determined by the ratio of protective seroconversion and the geometric mean titer (GMT) of anti-HBs obtained by id vaccine following the third vaccination. These parameters were also used in order to assess

the influence o sex and age on anti-HBs response. Sufficient seroconversion for protection was defined as a concentration of anti-HBs ≥ 10 IU/L[22].

The GMTs for anti-HBs were compared using the Mann-Whitney U test. The Fisher's exact test was used to compare seroconversion rates. Correlation analysis was used to examine the relation of vaccine and sex and age.

Results

The GMT for anti-HBs of infants and preschool children, measured eight weeks after the third vaccination, are shown in Table I and Figure 1. The GMT of infants was 753 IU/L; that of preschool children was 799 IU/L. There was no statistically significant difference between the anti-HBs GMT of infants and preschool children. The GMT of female infants (789 IU/L) was similar to that of male infants (717 IU/L). The GMT of female preschool children (996 IU/L) was also not significantly different from that of male preschool children (626 IU/L).

Table I: The Geometric Mean Titer (GMT) for Anti-HBs Measured Eight Weeks After Three 2 µg Doses Intradermal HB Vaccination

Groups	n	GMT (IU/L)
Infants	86	753.0*
Male	44	717.6
Female	42	789.2
Preschol children	101	799.3*
Male	48	626.3
Female	53	996.7

* There was no statistically significant difference between the anti-HBs GMT of infants and preschool children.

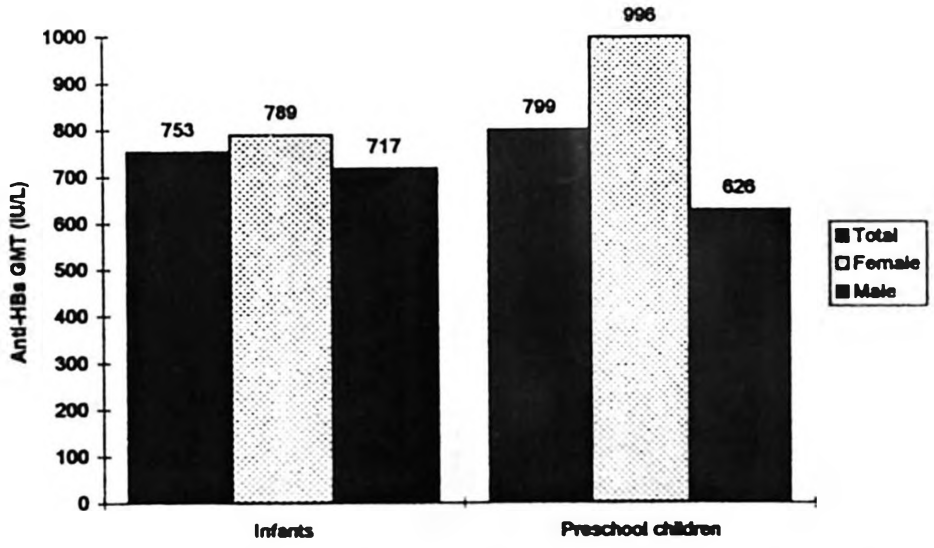

Fig. 1: The geometric mean titer (GMT) for anti-HBs of infants and preschool children measured eight weeks after third vaccination

The percentage of different anti-HBs titers in infants and preschool children are shown in Table II and Figure 2. Eight weeks after completion of vaccination, anti-HBs responses and protective anti-HBs responses (≥ 10 IU/L) developed in 94.2 and 93.0 percent of infants, respectively. Seroconversion to protective anti-HBs levels was achieved in all preschool children. The protective seroconversion rates of preschool children (100%) were significantly higher than those of infants (93%) (p = 0.0086). Seventy-two percent of infants and 91.1 percent of preschool children had anti-HBs titers higher than 100 IU/L. Furthermore, 43.0 percent of infants and 47.5 percent of preschool children had anti-HBs titers higher than 1000 IU/L.

Table II: The Percentage of Children (Infants and Preschool) with Different Anti-HBs Titers Eight Weeks After Third Vaccination

	Anti-HBs Titers (IU/L)			
Groups	≥ 1	≥ 10	≥ 100	≥ 1000
Infants (n = 86)	94.2	93.0	72.1	43.0
Male (n = 44)	93.2	90.9	69.1	42.8
Female (n = 42)	95.2	95.2	75.0	43.2
Preschool children (n = 101)	100	100	91.1	47.5
Male (n = 48)	100	100	85.4	39.6
Female (n = 53)	100	100	96.2	54.7

The protective seroconversion rates of preschool children were significantly higher than those of infants (p = 0.0086).

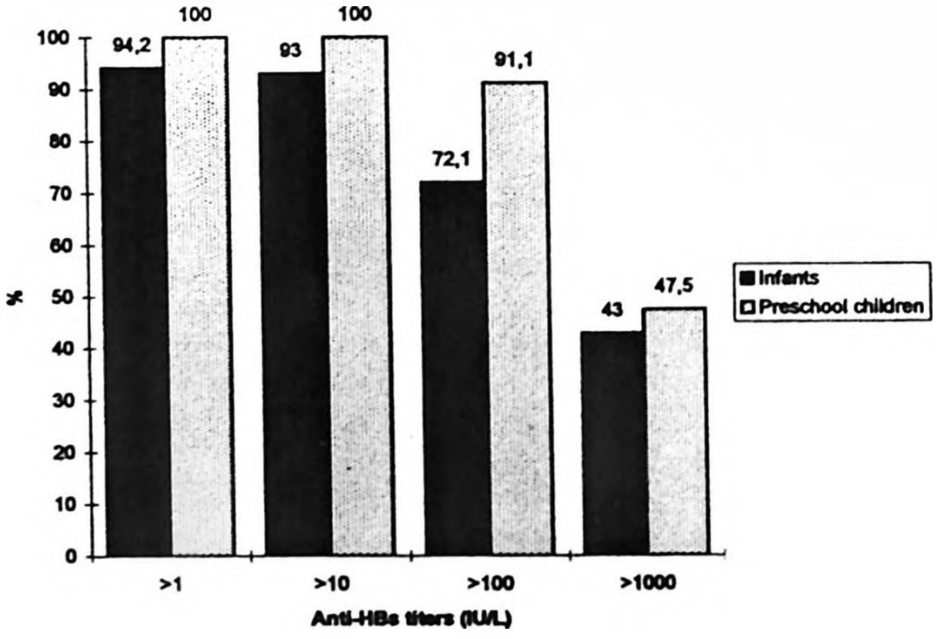

Fig. 2: The percentage of different anti-HBs titers of infants and preschool children eight weeks after third vaccination.

The GMT for anti-HBs and protective seroconversion rates of preschool children in various age groups are summarized in Table III. The GMT for anti-HBs and protective seroconversion rates of the various age groups were similar. No effect of sex and age on anti-HBs response of preschool children was determined.

Table III: The Geometric Mean Titer (GMT) of Anti-HBs and the Proportion of Preschool Children of Various Ages Who Achieved the Protective Level

			Seroconversion Rate	
Age Years	n	Anti-HBs GMT (IU/L)	≥ 10 IU/L	≥ 100 IU/L
0	86	753.4	93.0	72.1
1	11	694.3	100.0	91.0
2	19	881.1	100.0	94.8
3	12	741.3	100.0	91.7
4	23	649.5	100.0	87.0
5	15	1082.3	100.0	100.0
6	21	961.6	100.0	89.8

The GMT for anti-HBs and protective seroconversion rates were not found significantly different among the age groups.

There were no serious adverse experiences attributable to the vaccine, and no infant or preschool child was excluded from the study because of a serious reaction. Mild local tenderness and erythema were observed in 8.1 percent of infants. Persistent induration was detected in only one infant and hyperpigmentation was noted in 5.7 percent. Systemic complaints such as fever and hyperirritability were observed in 12.1 and 38.1 percent of infants respectively after the first or second doses, which were usually given at the same time as the DTP vaccine. However, these side effects were observed in only one infant after the third dose of hepatitis B vaccine when the DTP vaccine was not given.

Mild local tenderness and erythema were noted in 3.9 percent of preschool children and hyperpigmentation in 4.9 percent. Fever and irritability were observed in only one preschool child.

Discussion

Some investigators have reported that protective anti-HBs levels were achieved in 67-100 percent of adults with three or four low-dose id hepatitis B vaccines[11-19]. In the only study which was carried out in Turkey, the use of recombinant 4µ hepatitis B vaccine by id route at zero, one and six months in 101 adult volunteers achieved a 91 percent protective response rate[12]. However, there have not been enough observations and studies which reflect similar results in infants and children. According to these results, all preschool children achieved protective anti-HBs levels by administration of three doses of a 2 µg recombinant hepatitis

B vaccine by id route. However, the duration of protective levels is still unclear, although recent evidence suggests that a person who develops a higher anti-HBs titer is more likely to have long-term protective levels of the antibody two to three years longer than the ones who have lower anti-HBs titers[11, 23]. In this study, a high proportion of preschool children (91.1%) developed anti-HBs titers higher than 100 IU/L.

Therefore, it has been thought that long-term protection has been achieved in preschool children by using the id technique and low-dose recombinant hepatitis B vaccine. However, there is a need for large-scale and long-term prospective comparative trials to substantiate the economic and epidemiologic value of the id hepatitis B vaccination in preschool children.

The lower response of the infants to the hepatitis B vaccine compared with older children can be attributed to the immaturity of the immune system. So far, only one study has been carried out concerning id hepatitis B vaccine administration in infants. In that study, protective anti-HBs levels were achieved in 91 percent of the infants, and the anti-HBs GMT for infants was 312 IU/L following an id plasma-derived hepatitis B vaccine[20]. In our study, a recombinant hepatitis B vaccine was used and 93 percent of infants reached protective anti-HBs levels after id vaccination. The anti-HBs GMT for infants (753 IU/L) was extremely high. The differences observed in antibody responses may have been due to the different types of vaccines (recombinant vs plasma-derived hepatitis B vaccine).

Demographic factors such as age and sex may affect antibody response to the id vaccine[19]. It has been reported previously that the female responded better than the male[12]. However, anti-HBs responses of females were found similar to those of males in this study.

Adverse skin reactions such as local pruritus, pain, erythema, induration, and hyperpigmentation were reported after the id vaccine administration[11, 19, 20]. The thin epidermis of the infants makes id immunization technically difficult, and may cause adverse skin reactions to occur. In this study, the vaccines were well tolerated and there were no serious side effects in infants or preschool children. In 8.1 percent of infants and in 3.9 percent of preschool children, local reactions were observed. No patient was excluded from the study because of side effects.

It was concluded that the 2 µg recombinant vaccine by id route is safe and suitable for immunization of preschool children. The id route is technically difficult to administrate in infants and protective seroconversion rates are lower than these observed preschool children.

REFERENCES

1. Maynard JE, Kane MA, Alter MJ, Halder SC. Controls of hepatitis B by immunization: global perspectives. In: Zuckerman AJ (ed). Viral Hepatitis and Liver Diseases. New York: Alan R. Liss Inc; 1988: 967-969.
2. Report of a WHO Meeting. Prevention of liver cancer. Technical Report 691, World Health Organization, Geneva 1983: 8-9.

3. Bilgiç A, Sezer N, Uçarcı A. İzmir ili kan vericilerinde HBsAg'nin iki ayrı serolojik yöntemle araştırılması. Ege Üniv Tıp Fak Der 1982; 21: 717-720.
4. Uç A, Özsoylu Ş. Age-qrevalence of HBsAg positivity in children seen at Hacettepe Children's Hospital. Turk J Med Res 1992; 10: 264-266.
5. Değertekin H, Kestellioğlu F. The prevalence of HBsAg in healthy people and several liver diseases in Turkey. Asian Med J 1986; 29: 125-127.
6. Turhanoğlu M, Arıkan E. Güney Doğu Anadolu Bölgesinde değişik gruplardaki HBsAg ve antikorunun saptanması. D Ü Tıp Fak Der 1987; 1: 28-40.
7. Arıoğul S, Akalın E, Kanra T. HBsAg among Turkish blood donors. Infection 1987; 15: 456.
8. Kuru Ü, Şenli S, Türel L, Kuru N, Başkent A, Ulucaklı Ö. Age-specific seroprevalence of hepatitis B virus infection. Turk J Pediatr 1995; 37: 331-338.
9. Çakaloğlu Y, Ökten A, Yalçın S. Türkiye'de hepatit B virusu enfeksiyonu seroepidemiyolojisi. Turk J Gastroenterohepatol 1990; 1: 49-52.
10. Badur S. Ülkemizde viral hepatitlerin durumu (Viral hepatitle savaşım derneği raporu). In: Kılıçturgay K (ed). Viral Hepatit'94. İstanbul: Nobel Tıp Kitapevleri Ltd. Şti.; 1994: 15-37.
11. King JW, Taylor EM, Crow SD, et al. Comparison of the immunogenicity of hepatitis B vaccine administered intradermally and intramuscularly. Rev Infect Dis 1990; 12: 1035-1043.
12. Tekeli E, Balık İ, Kurt H, Kandilci S, Şenbil O. Intramuscular and intradermal administration of a recombinant hepatitis B vaccine. Türkiye Tıp Dergisi 1995; 1: 23-26.
13. Mok Q, Underhill G, Wonke B, Aldouri M, Kelsey M, Jefferies D. Intradermal hepatitis B vaccine in thalassaemia and sickle cell disease. Arch Dis Child 1989; 64: 535-540.
14. Toffler WL, Olenick JS, Wolf NE, Retzlaff ZH, Swanson JR, Kenny TA. The immunogenicity and safety of intradermal hepatitis B vaccine. J Fam Pract 1991; 33: 149-154.
15. Ronish RH, Diniega BM, Kelley PW, et al. Immunogenicity achieved by the intradermal hepatitis B vaccination programme for US Army soldiers in Korea. Vaccine 1991; 9: 364-368.
16. Sirinavin S, Muchacheap T, Khupulsup K, Inthraphuwasak W, Petchclai B. Intradermal hepatitis B virus immunization: immunogenicity and reactogenicity. Southeast Asian J Trop Med Public Health 1991; 22: 577-580.
17. Gonzalez ML, Usandizaga M, Alomar P, et al. Intradermal and intramuscular route for vaccination against hepatits B. Vaccine 1990; 8: 402-405.
18. Morris CA, Oliver PR, Reynolds F, Selkon JB. Intradermal hepatitis B immunization with yeast derived vaccine: serological response by sex and age. Epidemiol Infect 1989; 103: 387-394.
19. Rivey MP, Peterson J. Intradermal hepatitis B vaccination. DICP 1991; 25: 628-634.
20. Coberly JS, Townsend T, Repke J, Fields H, Margolis H, Halsey NA. Suboptimal response following intradermal hepatitis B vaccine in infants. Vaccine 1994; 12: 984-987.
21. Abbott Laboratories, Diagnostic Division Abbott Park, IL 60064, November 1991, List No. 2262.
22. Dienstag JL, Werner BG, Polk BF, et al. Hepatitis B vaccine in health care personnel: safety, immunogenicity, and indicators of efficacy. Ann Intern Med 1984; 101: 34-40.
23. Stevens CE, Toy PT, Taylor PE, Lee T; Yip HY. Prospects for control of hepatitis B virus infection: implications of childhood vaccination and long-term protection. Pediatrics 1992, 90· 170-173.