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ORIGINAL ARTICLE

Comparison of Immunogenicity of Low-Dose Intradermal Hepatitis B Vaccine with the Standard-Dose Intramuscular Vaccination in Young Healthy Iranian Adults

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Background and Aims: **Although hepatitis B vaccine reliably induces immunity against hepatitis B virus (HBV), the cost of intramuscular (IM) vaccination has limited its use, particularly in many developing countries. Intradermal (ID) vaccination has been proposed as a cost-saving alternative method for administration of hepatitis B vaccine. However, the effectiveness of ID vaccination needs to be assessed in different ethnic groups.**

Methods: **From September 2006 to March 2008, 185 healthy anti-HBc-negative medical and nursing students at Zahedan University of Medical Sciences who had no history of vaccination against HBV, smoking or hepatitis were evaluated. They were randomly categorized into two groups. In group I (n=91), low-dose (4 μg) recombinant hepatitis B vaccine (Euvax B, Korea) was given by intradermal route. In group II (n=94), the standard dose (20 μg) of the vaccine was administered intramuscularly at 0, 1, and 6 months. The groups were followed for a minimum of 7 months after the first vaccine dose and tested for anti-HBs titers by ELISA (Diasorin Bio Medica Kit, Saluugia, Italy).**

Results: **Seroprotective anti-HBs titers (titer >10 mIU/mL) were achieved in 79 (87%) students in group I and in 90 (96%) in group II (P=0.031). The difference was much pronounced when the two groups were compared for achieving an anti-HBs titer >300 mIU/mL (P<0.0001).**

Conclusions: **Although ID administration of 4-μg recombinant hepatitis B vaccine is effective, this route is less effective with lower immune response than the IM vaccination.**

Keywords: **Hepatitis B Vaccine, Immunogenicity, Intradermal Vaccination, Intramuscular Vaccination**

Introduction

Hepatitis B virus (HBV) infection-a silent killer-is a major cause of morbidity and mortality. It is a global health problem [1]. Current estimates are that two billion people have been infected worldwide of whom 360 million suffer from chronic HBV infection resulting in over 520,000 deaths from acute hepatitis B and 470,000 from cirrhosis or liver cancer [2-4]. HBV infection and its complications are among the most common diseases in Iran [3]. It is estimated that over 35% of Iranians have been exposed to HBV and almost 3% are chronic carriers [2, 3, 5].

A simple way to be protected against this dreadful disease is vaccination. Hepatitis B vaccination has been one of the success stories of the 20th century and has been extensively used in a wide range of groups throughout the world [6, 7]. The

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immunogenicity, efficiency, and safety profile of hepatitis B vaccine has been well established. More than 90% seroconversion has been achieved in adult populations consistently [3-5, 7]. Universal HBV vaccination has led to a significant reduction in the prevalence of hepatitis B and incidence of cirrhosis and hepatocellular carcinoma (HCC) worldwide [2-5]. Moreover, hepatitis B vaccination program has successfully reduced the prevalence of hepatitis B in Iran [4]. National mass vaccination of neonates against hepatitis B was started in 1991, but soon it was considered as a costly venture [8].

Intradermal (ID) vaccination has been proposed as a cost-saving alternative method for administration of hepatitis B vaccine to implement of mass vaccination of high-risk groups, particularly in developing countries [6-9]. Nonetheless, the effectiveness of ID vaccination needs to be assessed in different ethnic groups. There are a few studies about efficacy of ID vaccination in Iranian adults. The present study was conducted to compare the immunogenicity of a low-dose (4 µg) recombinant vaccine administered by ID route with the standard dose (20 µg) of intramuscular (IM) vaccination in young healthy Iranian population.

Patients and Methods

In this randomized clinical trial conducted from September 2006 to March 2008, 185 healthy anti-HBs-negative medical and nursing students at Zahedan University of Medical Sciences who had no history of vaccination, smoking and hepatitis were evaluated. All the students who had these inclusion criteria selected and then referred to Boo-Ali Hospital for evaluation. They were then allocated into two groups using a simple randomized method. Written informed consent was obtained from each participant. The Ethical Committee of Zahedan University of Medical Sciences approved the study protocol. Blood samples were collected and screened for anti-HBs titers by ELISA (Diasorin Bio Medica Kit, Saluugia, Italy). All of the tests were carried out in the Laboratory of the Research Center of Blood Transfusion Organization.

In group I (ID group), low-dose (4 µg) recombinant hepatitis B vaccine (Euvax B, Korea) was given by intradermal route. In group II (IM group), the standard dose (20 µg) of the vaccine was administered intramuscularly at 0, 1, and 6 months. Both groups were followed for a minimum of seven months. The anti-HBs antibody titers were measured in the two groups after four weeks of the last vaccine dose. A non-response was defined as anti-HBs antibody titers ≤10 mIU/mL; responders were those with antibody titer of ≥10 mIU/mL and ≤100 mIU/mL; high responders were those with anti-HBs titers ≥100 mIU/mL and ≤500 mIU/mL; those with titers ≥500 mIU/mL were considered hyper-responder.

All demographic and laboratory findings in the two groups were reviewed and compared. Statistical analyses were performed using SPSS, ver 11.0. Comparisons between geometric mean titers were made by *Student's t*-test. Comparisons between frequencies were performed by χ^2 test. P<0.05 was considered statistically significant.

Results

Of the 185 medical and nursing students studied, 91 (73 women, 18 men) were in group I (ID) and 94 (78 women and 16 men) were in group II (IM). The age of participants ranged from 18-22 years in ID vaccinated 18-23 in IM vaccinated groups. The mean age of IM group (19.9 years) was not different from that of the ID group (20.2 years). There was no difference in body mass index (BMI) between ID and IM vaccinated groups (21.76 νs. 21.96 kg/m2, respectively) too (Table 1).

Seroprotective anti-HBs titers (*i.e.*, >10 mIU/mL) were achieved in 79 (87%; 95% CI: 79.9%-93.8%) of 91 students who received ID doses and in 90 (96%; 95% CI: 91.7%-99.8%) of 94 students in the IM group (P=0.031) (Table 1). The difference was much pronounced when the two groups were compared for achieving an anti-HBs titer >300 mIU/mL. Among the IM vaccinated students, 95% had an antibody titer >300 mIU/mL while in the ID group, only one student had (P<0.0001). Sixty-two students (66%) of IM vaccinated group had a titer >500 mIU/mL (hyper-responder). None of the students in ID group were hyper-responder (Table 2).

Table 1. Immune response in the two studied groups.

	n	Mean ± SD	P value
Anti-HBs level (mIU/ML)			
IM group	94	655.35±276.74	< 0.001
ID group	91	113.20±93.73	
BMI			
IM group	94	21.96±2.52	0.615
ID group	91	21.76±3.01	
Age			
IM group	94	20.22±2.35	0.336
ID group	91	19.91±2.01	

BMI: body mass index; ID: intradermal; IM: Intramuscular; SD: standard deviation

Table 2. Immune response in the two studied groups.

Anti-HBs level (mIU/mL)	No. in ID group (%) n=91	No. in IM group (%) n=94
Non-responder (0-9)	12 (13)	4 (4)
Responder (10-99)	40 (44)	0 (0)
High responder (100-499)	39 (43)	28 (30)
Hyper-responder (500-1000)	0 (0)	62 (66)

Discussion

The present study was done to determine the efficacy of ID hepatitis B vaccination, as few studies from Iran [8-11] and other countries [6, 7, 12-14] found it an effective route of vaccination. Another objective was to compare the immunogenicity of ID compared to IM routes, keeping the host factors similar to minimize the effect of confounding variables. We found that the immunization rate was significantly correlated with the route of vaccine administration. Seroprotective anti-HBs titers were achieved in 79 (87%) students who received the low-dose of the vaccine by ID route as compared to 90 (96%) students who received the IM injection of a standard dose of the vaccine. Similar results were reported by Sunil and colleagues. They showed that the seroprotective rate (anti-HBs >10 mIU/mL) among 89 subjects in the ID group was 92.1% and that the geometric mean of the antibody titers in the group was 92.71 mIU/mL. Similarly, in the IM group, with a geometric mean of anti-HBs antibody titer of 331.66 mIU/mL, the seroprotection rate was 98.8%. They concluded that the ID route is less effective with lower immunogenicity than the IM route [14].

Similar results were observed by Coberly, *et al.* [13]. They reported a sub-optimal response following ID injection of hepatitis B vaccine in infants compared with the IM administration of the vaccine [13]. Our literature review, however, showed some benefit of ID compared to IM vaccination in terms of the seroprotection rate [6, 8-11, 15]. Ghabouli and his colleagues in Mashhad, northeastern Iran, showed that the overall seroprotection rate (anti-HBs level ≥10 mIU/mL) was 97.3% after ID vaccination and 98.6% after IM vaccination (P=0.99) [9]. A few studies from Iran in pediatric age group, have also revealed that ID vaccination results in a higher seroprotection rate than the IM vaccination [8, 10]. The mechanism of the higher efficacy of ID than IM route in active immunization in recent studies still remains unclear. It has been suggested that ID administration of antigen may activate specific epidermal cells and is capable of inducing an effective lymphocyte response. The concept of ID inoculation of vaccines has originated from observations of Thompson, *et al.* [16] who stated that modified epidermal cells present in dermis are antigen representing cells.

ID administration of hepatitis B vaccine has been repeatedly proposed in individuals with normal renal function and chronic renal failure [15]. Fabrizi and colleagues demonstrated that the immunization rate was significantly higher in ID group than the IM group and that it was correlated with the number of vaccine shots. They therefore, concluded that ID vaccination against HBV needs more frequent vaccine administration in dialysis patients [15]. Although, some reports showed that ID administration of hepatitis B vaccine is as effective as IM route, in our study, ID injection of the vaccine was less effective and provided lower immunogenicity than the IM vaccination.

A major limitation of our study was the small number of medical and nursing students who were available for the study. That was because many of them have received vaccine and should therefore be excluded from the study. We decided to evaluate all medical and nursing students who were studying at Zahedan Medical University, but only 185 fulfilled the inclusion criteria. On the other hand, our study did not show the benefit of ID compared to IM vaccination in terms of the seroprotection time, because we did not follow these students more than seven months. Unfortunately, most of comparative studies have not followed the vaccinees for a long period, say three to five years. All three studied which have followed the subjects for 2-3 years have reported no significant difference in the persistence of antibodies after ID and IM vaccination [7, 17, 18]. Since an antibody titer of more than 10 mIU/mL is considered protective, to determine whether the antibody level remains significantly higher in the IM vaccination after a long period, say 3-5 years after the primary vaccination, compared to the ID vaccination, we need to follow our subjects for at least five years. Furthermore, to determine the efficacy of ID vaccination in different ethnic groups, we suggest more studies in other provinces of Iran.

Conclusions

Low-dose ID vaccination is less effective with lower immunogenicity than IM route. Therefore,

ID vaccination is not the preferred route for hepatitis B vaccination.

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