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ORIGINAL ARTICLE

COMPARATIVE EFFECT OF INTRADERMAL AND INTRAMUSCULAR INJECTIONS OF HEPATITIS B VACCINE

Hassan Afzali MD*, Gholam-Reza Vali MSc**, Ahmad Khalifeh-Soltani MD*

*Department of Infectious Diseases, **Department of Biochemistry, Kashan University of Medical Sciences, Kashan, Iran

Background – **Hepatitis B virus is one of the most common causes of chronic liver disease, cirrhosis and liver carcinoma, and prophylaxis with vaccination is of utmost importance. The present study was conducted to compare the effectiveness of intradermal and intramuscular injection of hepatitis B vaccine.**

Methods – **Two-hundred female high school students entered this double-blind randomized clinical trial performed in Kashan (a city in the center of Iran) in 1996–97. A 5-mL blood sample was obtained and checked for hepatitis B surface antigen (HBsAg) and antibodies to the HBsAg (HBsAb) using an enzyme-linked immunosorbent assay (ELISA). Subjects were allocated to one of three age groups and randomly assigned to receive intramuscular (control; 1 mL recombinant hepatitis B vaccine) or intradermal (case) vaccine (0.1 mL recombinant hepatitis B vaccine) in the deltoid region at months 0, 1, and 6. Three weeks after the last vaccination, the HBsAb level was measured by ELISA.**

Results – **Intramuscular injection resulted in 97.6% positive, 1.2% mild, and 1.2% negative responses, respectively, whereas intradermal injection resulted in 93.7% positive, 2.1% mild, and 4.2% negative responses, respectively. This difference was not statistically significant ($p = 0.23$).**

Conclusion – **Due to a very small difference in the effectiveness of the two injection methods and the cost-effectiveness of the intradermal injection, intradermal injection could be safely substituted for intramuscular injection.**

Keywords ⟩ antibody ⟩ hepatitis B vaccine ⟩ intramuscular ⟩ intradermal

Introduction

Hepatitis B virus (HBV) causes liver inflammation and necrosis. The route of entry of virus into the body is blood, sexual contact, and mother to fetus.[1] Approximately 300 million carriers exist worldwide and about one million are infected in the United States.[2] Vaccination is the most important method of prophylaxis and prevention of complications of hepatitis B.[3]

The rate of Australian antigen (HBsAg) in healthy individuals in Iran is between 1.4 and 6%.[4] A study among 2-year-old Mongolian children reported a prevalence of HBV carriage of 14%. The authors found an unexpected 40% of subjects in rural Bayanhongor Aimag positive for hepatits B surface antigen (HBsAg).[5]

Approximately 300 million of the world population with high risk are affected by chronic hepatitis B, a significant proportion of whom eventually suffer from liver cell carcinoma.[6] In areas with low, intermediate and high endemicity, universal vaccination seems to be economically reasonable. Investigators have compared the effectiveness of intramuscular (IM) and intradermal (ID) injections as well as their costs, and strongly suggest that the intradermal route, in which one-tenth of the IM injection is administered, is best.[7]

In a study in Spain in 1990, it was demonstrated

• **Correspondence:** *H. Afzali MD, Department of Infectious Diseases, Kashan University of Medical Sciences, Kashan, Iran. Fax: +98-361-558900, E-mail: beheshti_hospital@hotmail.com.*

Table 1. Distribution of students receiving intramuscular and intradermal injections of hepatitis B vaccine.

Type of injection	School grade			
	1	2	3	Total
Intramuscular	32 (38.3%)	32 (39.5%)	18 (22.2%)	82 (100%)
Intradermal	37 (38.9%)	37 (38.9%)	21 (22.2%)	95 (100%)

that as much as a 97% positive response rate might be observed using the ID method, while this rate was limited to only 78% for the IM method.[8] In an investigation in Canada in 2000, seroconversion rates by ID vaccination at 9 month and 1 year postvaccination were 99% and 96%, respectively, and by IM method were 95% and 96%.[9] Since there is great differences in the rate of immunity in available studies and since ID injection seems to be more economic for developing countries and there is no experience on these subjects in our country, the present study was conducted to compare the efficacy of there two methods.

Unfortunately, there has been no extended research program on the route of hepatitis B vaccine administration in Iran. Indeed, if we prove the same effectiveness for ID as IM injection, then ID vaccination can safely employed in our immunization program.

Materials and Methods

Two hundred female 1st- through 3rd-year high school students entered this double-blind, randomized clinical trial in Kashan (a city in the center of Iran) in 1996–97. After our study was explained, initial data including age, marital status, previous history of jaundice, level of education (1st, 2nd, or 3rd year of high school), and signs related to acute hepatitis were all recorded. None of the students had a previous history of hepatitis B vaccination. A 5 mL blood sample was obtained and assayed for HBsAg and antibodies to HBsAg (HBsAb) using an enzyme-linked immunosorbent assay (ELISA) method (Behring kit, Germany).

Students were grouped by age: 13–16 years, 16–19 years, and 19–22 years old. Subjects in each group were randomly assigned to receive IM (control) or ID (case) vaccine. Both students and researchers were unaware of the route of vaccination and vaccination was given according to previously determined code numbers. In control subjects, 1 mL of recombinant vaccine (Herber Biotec,Cuba) was deeply injected into deltoid muscle using needle No. 21 at 0, 1, and 6 months. In case subjects, 0.1 mL of the same vaccine was intradermally injected in the same region using needle No. 24 at the same time intervals.

Three weeks after the last vaccination, a 5 mL blood sample was collected and sent to the Central Laboratory of Iran Blood Transfusion Center for measurement of HBsAb level using ELISA; a positive result was defined as a titer of more than 100 IU/L, a mild-positive result was defined as a titer of 10–100 IU/L, and a negative result as a titer of less than 10 IU/L. Samples were also tested for HBsAg since there was a possibility of natural infection during the course of the study. Finally, data were analyzed by Chi-squared and Fisher's exact tests.

Results

Of the 200 cases, 10 were excluded because they were positive for HBsAg or HBsAb. The mean age (± standard deviation [SD]) of students receiving IM and ID vaccination was 15.6 ± 2.5 and 16.1 ± 2.1 years, respectively ($p = 0.995$). In the control group, 14 dropped out of the study due to leaving school, irregularity or absence in the second and third rounds of vaccination, but there was still no statistical difference (Table 1; $p = 0.995$). There was no statistically significant difference in HBsAb response in the two groups (Table 2; $p = 0.23$).

Table 2. Distribution of antibodies to hepatitis B surface antigen (HBsAb) in students receiving intramuscular and intradermal injections of hepatitis B vaccine.

Type of injection	HBsAb			
	Positive	Mild-positive	Negative	Total
Intramuscular	79 (97.6%)	1 (1.2%)	1 (1.2%)	81(100%)
Intradermal	89 (93.7%)	2 (2.1%)	4 (4.2%)	95 (100%)

Discussion

IM injection led to positive, mild and negative antibody responses in 97.6%, 1.2%, and 1.2% of cases, respectively. For intradermal injection, these figures were 93.7%, 2.1%, and 4.2%, respectively. In a study conducted by McMaster et al several volunteers received intradermal recombinant vaccine in four doses separated by 1, 2, 6 and 8 months the effect of the vaccine, determined by HBsAb level, showed that approximately 90% of subjects had titers exceeding 10 IU/L. The remaining 10% received one booster vaccine one months following the last injection, which caused a rise in antibody titer to protective levels in 41% of cases.[10] These results are similar to our findings.

Gonzalez et al demonstrated that, using intradermal vaccination, there was up to 97% positive response, while using IM vaccination, there was only a 78% positive response.[8] Brayan and colleagues showed that three doses of recombinant vaccine at intervals of 1 and 6 months among individuals aged 16 to 64 years resulted in antibody production in 55 to 81% of individuals.[11] The difference in antibody response appears to be related to the age of subjects (16.1 ± 2.1 years in our study vs 16 to 65 years). The difference can be explained by the lower response in age groups exceeding 40 years. [3]

Kurugol et al reported that the intradermal injection produced a 97% antibody response;[12] however, in a study in Sweden in 1999, the seroconversion rate to protective HBsAb levels after three doses of intradermal vaccine was 68% and after four doses, 89%.[13] In an investigation in Canada in 2000, seroconversion rates at 9 months and 1 year after intradermal vaccination were 99% and 96%, respectively, and after IM vaccination were 95% and 96%, respectively.[9] In another study, 1 mL of IM vaccine was injected into 108 subjects while 0.1 mL of intradermal vaccine was used in 110 subjects in four rounds of injection. Antibody production following the immunization period was more than 10 IU/L.[14] The differences in antibody level between our study and others may be due to the possible effect of repeated vaccine (4 vs 3).

In a study using three intradermal plasma vaccine injections, the HBsAb level remained at 10 IU/L at 30 months after the last injection.[15]

In another study by Baryan, subjects who received complete intradermal or IM vaccine injections (1, 2, and 6 months) but did not develop a favorable immune response (HBsAb < 10 IU/L), received a booster injection similar to their previous injections.[16] Of these individuals, 50% achieved serum HBsAb levels exceeding 10 IU/L; however, the type of booster injection had no effect on immunization.

Considering the difference in the immune factors of different tissues, the immune responses in different tissues are different. Antigens entering through skin, mucus surfaces or parenchymal organs (muscular injection) and connective tissues are directed toward the lymph nodes, where the immune response occurs. Thus, skin, which can create and protect local immune and inflammatory reactions, is considered an important organ in defense responses. When an antigen enters the epidermis (intradermal injection), it is picked up and processed by Langerhans cells. These cells migrate through lymphatic dermal vessels to lymph nodes and introduce the antigen to T- and CD4+-lymphocytes. Generally, the results of this type of response are more cellular and mediated by the activities of T-lymphocytes (e.g. increment of late sensitivity) and humoral immune response does not become very active.

Antigens entering the body through the skin induce immunoglobulin (IgA) secretion, which is mainly detected in skin secretions such as sweat. These secretions play an important role in controlling microbial infection in the skin. On the other hand, antigens entering the lymphatic network are directly picked up by antigen-presenting cells, which in turn produce antigens that are capable of activating humoral immunity. Hence, once the antigen has directly entered the body (subdermal injection), it can be distributed to a wider population of lymphocytes, thus causing more humoral response.[17]

The Iranian Ministry of Health and Pasteur Institute have reported a mean administration rate of 6 million doses of vaccine (1 mL) per year in Iran. Given a cost of 25,000 Rls per dose for IM (1 mL) and 2,500 Rls for intradermal (0.1 mL) vaccines, the intradermal injection saves more than 135 billion Rls per year.

From these facts, two conclusions can be drawn:

1. Given the insignificant difference between the injection methods, the cost of intradermal injection (0.1 mL), the possibility of increasing the target population with this method, and the significant difference in the rate of effectiveness in other studies, we suggest that

similar studies should be conducted in other centers. If their results are consistent with ours, intradermal injection could be safely substituted for IM injection (if it is accessible).

2. Further studies are required to determine the duration of vaccine effectiveness, the need for booster injections, and the appropriate time of injection.

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