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A Randomized Trial for Evaluating Prophylactic Effect of Intradermal and Intramuscular Hepatitis B Vaccine

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Abstract

Background: Hepatitis B virus is one of the most common causes of chronic liver diseases. Vaccination is the best way of prophylaxis and is of utmost importance. This study was conducted to compare the prophylactic effect of intradermal and intramuscular injection of hepatitis B vaccine.

Methods: A blind randomized clinical trial was performed among subjects who presented to the infectious diseases clinics to receive HB vaccine in Mashhad, north east Iran, during 2002- 2004. Eighty men and women who were HBs Ag & HBs Ab negative were randomly received 0.1 ml intradermal (study group) or 1ml intramuscular (control group) vaccine. The vaccine was injected into the deltoid region at months 0, 1, and 6. One month later, the HBsAb level was checked. The levels less than 10IU/L, 10-100 IU/L and more than 100 IU/L were defined as negative, mild positive and strong positive responses, respectively.

Results: Intramuscular and Intradermal injections resulted in 95%, 87.5% strong positive, 2.5%, 7.5% mild positive and 2.5%, 5% negative responses respectively. Mann-whitney and Fisher's Exact Test showed the difference between results was not statistically significant ($P>0.05$).

Conclusion: Due to small difference in the effectiveness of these two methods and the cost effectiveness of intradermal injection, this route could be substituted for intramuscular injection.

Keywords: *Hepatitis B vaccine, intramuscular, intradermal, effectiveness, HBs antibody*

Introduction

Hepatitis B virus (HBV) infection is a global public health problem. It is estimated that there are 2 billion individuals with serological evidence of hepatitis B and more than 300 million HBV carriers in the world, of who over 250000 die annually from HBV-related liver diseases (1). The prevalence of HBV carriers varies from 0.1 percent to 2 percent in low prevalence areas (The United States and Canada, Western Europe, Australia and New Zealand), to3-5 percent in intermediate prevalence areas (Mediterranean countries, Japan, Central Asia, Middle East, Latin and South America) to 10-20 percent in high prevalence areas (Southeast Asia, China and sub-saharan Africa) (1, 2). The rate of HBs antigen in healthy individuals in Iran has been between 1.4 and 6 percent (3).

Despite advances in antiviral therapy, only a minority of patients with chronic hepatitis B will have a sustained response, thus primary prevention by vaccination to increase herd immunity remains the main thrust in the control of hepatitis B virus infection(4). Currently available hepatitis B vaccines are extremely safe and have efficacy of > 90 percent (5).

A positive immune response to the vaccine is defined as the development of hepatitis B surface antibody at a titer of ›10IU/L (6). Investigators have compared the effectiveness of intramuscular (IM) and intradermal (ID) injec-

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tions as well as their costs, and suggest that the intradermal route is better (7). This result is obtained from other studies for example in a study in Spain in 1990; positive responses were 97% for ID method and 78% for IM method (8). In contrast Arbizu et al. in a study in 66 non-cirrhotic hepatitis C patients showed that sero-conversion (antibody level >/=10 mIU/ml) in the intramuscular group was reached by 20%, 40% and 72% of patients at days 15, 30 and 60 compared to 48% and 36% for the intradermal group. Additionally, levels rose more rapidly in the intramuscular group (P= 0.004). Their results do not support the use of intradermal route of immunization against HBV in hepatitis C virus (HCV) infected patients (9). Since there is difference in the rate of immunity in available investigations and ID route is economic for developing countries, this study was conducted to compare the effectiveness of these two methods.

Materials and Methods

During 2002-2004 from each men and women between 16 to 45 yr old referring to the infectious diseases clinics to receive HBV vaccine, 5 ml blood sample was obtained and checked for HBsAg and HBsAb by using ELISA test in Mashhad. Informed consent was obtained from the subjects with negative tests. Eighty persons entered this blind randomized trial in two groups (study or ID group and control or IM group) with forty members in each one. The members of study and control groups were selected randomly by using random digits table. Initial data including age and sex, were recorded. They had not previous history of HB vaccination. In control group, 1ml of recombinant vaccine was injected into deltoid and in study group 0.1ml of recombinant vaccine was intradermally injected in the same region on the usual schedule of 0,1,6 months. The subjects and vaccinator knew about this process but the laboratory personnel did not know about route of vaccination. Four weeks after the last vaccination, their serums were collected and evaluated for titer of HBsAb. Strong positive result was defined as a titer of more than 100IU/L, mild positive as a titer of 10-100IU/L and negative test as a titer of less than 10IU/L. Finally, the data were classified and analyzed by SPSS version 11.5 using Fisher's Exact Test and Mann whitney U test.

Results

The mean age (±SD) of the subjects, receiving IM & ID vaccines were 32.2±6.4 and 29.0±7.0 years, respectively. Strong positive, mild positive and negative responses in ID group (study group) were seen in 35 (87.5%), 3 (7.5%) and 2(5%) of them and in IM group (control group) were seen in 38(95%), 1(2.5%0 and 1(2.5%) of them respectively. There was no statistically significant difference in immunity response between study and control groups) (Table1, 2).

Table 1: Distribution of HBs antibodies in subjects receiving intramuscular and intradermal injections of HB vaccine

Route of inoculation(groups)	No. (%) of negative response	No.(%) of positive response
IM inoculation(control group)	1(2.5)	39(97.5)
ID inoculation(study group)	2(5)	38(95)
Total	3(3.75)	77(96.25)

Fisher's Exact Test: (1-sided) P= 0.5

Table 2: Comparison of the ranks of response rates to HB vaccine in IM and ID groups

Route of injection	No.	Mean rank	Sum of ranks
Intradermal group	40	39.01	1560.5
Intramuscular group	40	41.99	1679.5
Total	80	-	-

Mann-whitney: Z=-1.169, *P*=0.24

Discussion

According to WHO information, 5-10 percent of the populations will not response to currently available IM route vaccine (5). Thus other ways to enhance immunogenicity of HBV vaccine should be studied. A number of methods such as vaccination via ID route have been proposed to reduce the non-response rate of conventional vaccination (5). Rahman et al. reported that Intradermal inoculation appears to be more immunogenic than intramuscular injection, but technically is more difficult to administer (10). Fabrizi et al. revealed that increased efficacy of ID inoculation was also evident in IM vaccine nonresponders (11).

Following our study in healthy persons who received HBV vaccine, IM vaccine injection led to strong positive, mild positive and negative responses in 95%, 2.5% and 2.5% of cases, respectively. For intradermal route, these figures were 87.5%, 7.5% and 5%, respectively. Statistically, IM and ID vaccine injections led to similar responses. Our findings are similar to those of Mc Master's in the United States (12). Mc Master et al. showed that 90% of subjects receiving four doses ID route vaccine separated by 1, 2, 6, 8 mo, had titers exceeding 10IU/L.

In the study by Brayan et al. about ID vaccination in individuals 16-64 years old, antibody production was revealed in 55 to 81% of subjects (13). Ghabouli et al. and Afzali et al. compared the effectiveness of HB vaccine in ID and IM route vaccination groups (14, 15). The overall seroprotection rates for ID vaccination groups, were not different from that of IM vaccination groups.

Das et al. in a randomized trial among health care workers demonstrated intradermal route for HBV vaccine had similar immunogenic efficacy as the conventional intramuscular route (16).

Kurugol et al. studied low-dose intradermal administration of recombinant hepatitis B vaccine in children. In this 5 yr follow up study 97% of the children developed anti-HBs antibodies higher than or equal to 10 mIU/ml (17).

Lankarani et al. in Iran concluded that intradermal vaccination with 20% of standard dose is as effective as IM vaccination when evaluated 18 mo after the first dose (18).

Egemen et al. concluded that intradermal administration of 2 micrograms recombinant hepatitis B vaccine is safe and effective in infants and preschool children, and may be an acceptable, less expensive alternative to full-dose IM vaccination for mass immunization, especially in developing countries (19).

Some investigators reported low dose intradermal and high dose intramuscular hepatitis B vaccination in patients with chronic hemodialysis (20, 21), CAPD (22), predialytic chronic renal failure (23), and among HIV-positive subjects (24) had similar results.

According to our survey and other studies explained above, HB vaccination via ID route had immunogenic efficacy as the conventional intramuscular route. Some investigators revealed that after ID vaccination seropositive antibody levels fell faster (25), the finding was not showed by others (18, 22). However the long term efficacy of ID route vaccination must still be studied. Some investigators reported ID route vaccination leads to production of variable HBs Ab lower than those followed IM route vaccination. Various amounts and differences in antibody levels among numerous studies about ID route vaccination may be due to:

1) The possible effect of repeated vaccine (more than three times). In a study, subjects who received complete ID vaccine injections (1, 2, 6 mo) but did not develop seroconversion with antibody levels more than 10IU/L, when

received a booster ID injection, 50% achieved serum HBsAb levels exceeding 10IU/L .

2) More humoral response followed IM injection. Considering the difference in the immune factors of different tissues, the immune response in different tissues is not similar. Antigens entering through skin, mucus membranes, or parenchymal organs (IM injection) are directed toward the lymphatic network, where the immune response especially humoral type occurs. When an antigen enters the epidermis (ID injection), it is picked up and processed by langerhans cells; these move to lymph nodes and present the antigen to T and CD4+ lymphocytes. Thus their responses are more cellular and humoral response is not very active.

3) Vaccine dosage: According to the results of some studies (20), strong seroconvesion occurs when followed vaccination via ID route using higher dose vaccine (double dose or more). Thus, increasing intradermal vaccine dose probably leads to produce higher antibody levels. However, this theory must be studied and established in future.

Finally, we concluded that:

Intradermal injection could be safely substituted for injection via IM route because of insignificant difference between the IM and ID immune responses lower cost of ID injection and the possibility of increasing the candidate individuals to receive vaccines.

Due to less expensive ID vaccine comparing IM one, mass immunization especially in developing countries may be acceptable as an alternative method.

Further investigations are required and necessary to determine the need for repeated injections (more than 3 times) at first 6 mo period, booster injections, best time of booster injections, appropriate intervals between them and duration of vaccine efficacy .

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References

1. Maynard JE, Hepatitis B: Global importance and need for control. *Vacc*. 1990; **8:** 18-20
2. Kim WR, Ishitani MB, Dickson ER. Rising burden of Hepatitis B in the United States. Should the other virus be forgotten? (Abstract). *Hema*. 2002; **36:** 222.
3. Shaikholeslami F. Australian antibody and antigen infection at Iranian dialysis centers [Doctorate thesis] .Department of public Health. Tehran University of medical sciences, Iran; 1968.
4. Mast EE, Alter MJ, Margolis HS. Strategies to prevent and control hepatitis B and C virus infections: A global perspective. *Vacc*. 1999; **17:** 1730-35.
5. World Health Organization. Global Immunization Coverage-Expanded program on Immunization (EPI) - Hepatitis *B.vaccine*. 1996.
6. Hadler SC, Francis DP, Maynard JE, Thompson SE, Judson FN, et al. Long term immunogenicity and efficacy of hepatitis B vaccine in homosexual men. *N Engl J Med*. 1986; **315:** 209.
7. Beutels P. Economic evaluations of heaptitis B immunization: a global review of recent studies (1994-2000). *Heal Econ*. 2001; **10:** 751-74.
8. Gonzaleze ML, Usandizaga M, Alomar P, Salva F, Martin F, Erroz MJ, Lardinois R. Intradermal and intramuscular routes for vaccination against hepatitis B.*Vacc*. 1990; **8:** 402-5.
9. Arbizu EA, Marugan RB, Grijalba JY, Serrano PL, Grande LG. Intramuscular versus intradermal administration of anti-hepatitis B vaccine in non-cirrhotic heaptitis patients. *Vacc*. 2003; **(21-22):**2747-50.

10. Rahman F, Dahmen A, Herzog-Hauff S, Wulf O. Böcher, Peter R, et al. Cellular and humoral immune responses induced by intradermal or intramuscular vaccination with the major hepatitis B surface antigen. *Hepa*. 2000; **31:** 521-27.
11. Fabrizi F, Andrulli S, Bacchini G, Corti M, Locatelli F. Intradermal versus intramuscular hepatitis B revaccination in non-responsive chronic dialysis patients: A prospective randomized study with cost-effectiveness evaluation. *Neph Dial Tran*. 1997; **12:** 1204-10
12. Mac Master KR, Ropert JK, Carter JB, Intradermal hepatitis B vaccination in a 30 bed primary care hospital; experience with a recombinant vaccine in a four-dose schedule. *Am Inf Con*. 1993; **21:** 283-8.
13. Brayan JP, Sjogren M, Igbal M. Comparative trial of low dose intradermal, recombinant and plasma-derived hepatitis B vaccines. *Infect Dis*. 1990; **162:** 789-93.
14. Ghabouli MJ, Sabouri AH, Shoeibi N, Bajestan SN, Baradaran H. High seroprotection rate induced by intradermal administration of a recombinant hepatitis B vaccine in young healthy adults: comparison with standard intramuscular vaccination. *Eur J Epid*. 2004; **19(9)**: 871-5.
15. Afzali H, Vali GR, Khalifeh-Solati A. Comparative effect of intradermal and intramuscular injections of hepatitis B vaccine. *Arch Iran Med*. 2003; **6(1)**: 9-12.
16. Das HS, Sawant P, Shirhatti RG, Vyas K, Vispute S, Dhadphale S, et al. Efficacy of low dose intradermal hepatitis B vaccine: results of a randomized trial among health care workers. *Trop Gastroenterol*. 2002; **23(3)**: 120-21.
17. Kurugol Z, Erensoy S, Aksit S, Egemen A, Bilgic A. Low-dose intradermal administration of recombinant hepatitis B vaccine in children: 5-yr follow-up study. *Vacc*. 2001; **19(28-29):** 3936-39.
18. Lankarani KB, Taghavi AR, Agah S, Karimi A. Comparison of intradermal and intramuscular administration of hepatitis B vaccine in neonates. *Ind J Gastroenterol*. 2001; **20(5):** 212-14
19. Egemen A, Aksit S, Kurugol Z, Erensoy S, Bilgic A, Akilli M. Low-dose intradermal versus intramuscular administration of recombinant hepatitis B vaccine: a com parison of immunogenicity in infants and preschool children. *Vacc*. 1998; **16(16):** 1511-15.
20. Roozbeh J, Moini M, Lankarani KB, Sagheb MM, Shahpoori S, Bastani B. Low dose intradermal versus high dose intramuscular hepatitis B vaccination in patients on chronic hemodialysis. *ASAIO J*. 2005; **51(3):** 242-45.
21. Charest AF, McDougall J, Goldstein MB. A randomized comparison of intradermal and intramuscular vaccination against hepatitis B virus in incident chronic hemodialysis patients. *Am J Kidney Dis*. 2000; **36(5):** 976-82.
22. Chau KF, Cheng YL, Tsang DN, Choi KS, Wong KM, Chak WL, et al. Efficacy and side effects of intradermal hepatitis B vaccination in CAPD patients: a comparison with the intramuscular vaccination. *Am J Kidney Dis*. 2004; **43(5):** 910-17.
23. Somboonsilp W, Eiam-Ong S, Tungsanga K, Tirawatanapong T. Immune response of intradermal hepatitis B vaccination at lower dose versus intramuscular vaccination at double standard dose in predialytic chronic renal failure patients. *J Med Assoc Thai*. 2003; **86(12):** 1122-27.
24. Ristola MA, Vuola JM, Valle M, von Reyn CF. Antibody responses to intradermal recombinant hepatitis B immunization among HIV-positive subjects. *Vacc*. 2004. 25; **23(2):** 205-9.
25. Milkowski A, Wyrwicz G, Kubit P, Smolenski O. Comparison of anti-HBV vaccine efficacy given intradermally and intramuscularly in hemodialysis patients. *Przegl Lek*. 2000; **57(11):** 628-34.