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Original Article

Comparison of Low Dose Intradermal with High Dose Intramuscular Hepatitis B Vaccination in Hemodialysis Patients

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ABSTRACT

Background:
Hemodialysis patients have a low immune response to the hepatitis B (HB) vaccine. The method of administration plays an important role in immune response establishment. This case control study compares the efficacy of intradermal (ID) and intramuscular (IM) injection methods for the HB vaccine.

Materials and Methods:
This study was undertaken in hemodialysis centers. We recruited 50 patients after excluding those with histories of previous HB vaccination, immunosuppressive therapy, and who were positive for HBsAb, HBsAg, and HCV antibody. Patients were randomly assigned to receive HB vaccine by either the ID or IM injection methods. The timeline for vaccine administration was 0, 1, 2 and 6 months for both groups. The ID group received 2 µg of EngerixB in both the right and left anterolateral forearms, for a total dose of 4 µg; the IM group received 20 µg in two sites in the deltoid muscle, for a total dose of 40 µg. We measured HBsAb titers at the third and seventh months following the first doses of HB vaccine.

Results:
In the third month after the first HB vaccination,40.4% of the patients reached HBsAb levels of at least 10 mIU/ml in the ID group versus 60.9% in the IM group. At the seventh month following the first HB vaccination, 68% of patients reached HBsAb levels of at least 10 mIU/ml in the ID group versus 68% in the IM group. However the mean HBsAb titer in the ID group was 459±323.8 versus 294.6±277.5 mIU/ml in the IM group.

Conclusion:
There was no significant relation between seroconversion rates for both injection methods. However the mean titers of HBsAb for both the third and seventh months after the first HB vaccination in the ID group were more than the IM group. The cost for the low dose HB vaccine in the ID group is less than the high dose vaccine for the IM group. Thus, it is beneficial to use the ID low dose HB vaccine for underdeveloped countries.

Keywords: Intradermal vaccination; Hepatitis B; Hemodialysis

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INTRODUCTION

A protective level of immune response after hepatitis B (HB) vaccination is defined as an anti-HBs titer greater than 10 mIU/ml. It has been estimated that 40%-50% of end stage renal disease (ESRD) patients who undergo hemodialysis do not develop antibody response to HB vaccination(1). Hence, these patients have a higher risk of acquiring HB disease. Vaccines should be administered either as a high dose intramuscular (IM) or by the intradermal

(ID) method. The initial reports regarding the ID method of HB vaccination have not shown a high seroconversion rate; however, these studies have used relatively low doses of HB vaccine(2). Recently 70%-100% seroconversion rates have been reported in hemodialysis patients by the ID method of administration(3). In a recent study the reported recombinant HB vaccination by ID method, which includes administration of 5 µg every two weeks with the intent to achieve a titer greater than 1000 mIU/ml or total of 52 doses, has achieved a response rate of 97.6%(4).

This trial compared the efficacy of a more convenient method of ID versus IM HB vaccination in ESRD patients undergoing routine hemodialysis.

MATERIALS AND METHODS

Patient selection

This case control study compared the efficacy of ID low dose (4 µg) to IM high dose (40 µg) HB recombinant vaccine. The study was undertaken at four hemodialysis centers: Imam Reza, Imam Hosein, Imam Sadegh, and Imam Sajjad hospitals in Mashhad, Iran over a one year period, from 2010-2011.

The Ethics Committee of Mashhad University of Medical Sciences approved the protocol of study,and participants signed informed consents for this study.

The study participants consisted of 50 ESRD patients, ages 16 to 64 years. There were 32 males and 18 females under chronic hemodialysis treatment who were not participants in the regular HB vaccination scheme. Participants underwent bicarbonate hemodialysis for 3-4 hours duration, three times per week. Prior to study entry, baseline serum samples were obtained from participants. Serologic tests that consisted of HBsAg, anti-HBc, HBsAb (IgG), and anti-HCV were measured by a second generation ELISA test. The HIV antibody test was measured by commercially available kits. Patients who were seronegative for all of these tests were selected for study participation.

We evaluated the blood transfusion histories for each patient and determined that no patient had a history of blood transfusion or intravenous drug abuse. In all patients, the hematocrit values were maintained between 30% and 35% by administration of erythropoietin.

Hepatitis B (HB) recombinant vaccine

Patients randomly received the HB vaccination by either the ID or IM methods.

Vaccinations were given in each hemodialysis center.

For the ID method, 25 chronic dialysis patients received a full course of HB vaccination given as four doses of 4 µg (0.2 ml) Engerix B in two separate sites, the right and left anterolateral forearms. A standard disposable 1 ml insulin syringe with a 25-gauge needle was used to administer the vaccine. These individuals were inoculated at months 0, 1, 2 and 6. A visible cutaneous bleb was considered as an evidence of the ID inoculation. All ID vaccinations were given by an infectious diseases assistant.

The IM method was administered to 25 chronic dialysis patients. Patients completed a full course of vaccination that consisted of 4 doses of 40 µg (2.0 ml) Engerix B. Injections were given in two sites in the deltoid muscle of the arms by a standard disposable 1 ml syringe with a 21-gauge needle. These individuals were inoculated at months 0, 1, 2 and 6.

Determination of antibody response

Antibody levels were checked at three and seven months after the first dose of vaccination. After completion of the vaccination schedule, titers of IgG HBsAb were checked by standardized microparticle ELISA at the Immunology laboratory of Imam Reza Hospital. The tests were performed with one kit and by one laboratory technician. Anti-HBs levels of 10 mIU/ml or more were considered positive for seroconversion. The presence of adverse effects after vaccination were monitored for all patients. Patients were asked to report any symptoms and signs that occurred during three days after each vaccination.

Statistical analysis

This was a descriptive analysis that reported the frequency, mean, and standard deviation. The Mann Whitney test was used to determine the relation between HBsAb and Hemodialysis duration. P-values less than 0.05 were considered significant. Statistical analyses were performed by using SPSS (Version 11.5).

RESULTS

There were 25 patients randomly chosen to receive the ID vaccination method, 19 males and 6 females who had a mean age of 37.5 years. All patients survived during the study. At three months after the first vaccination, 13 patients had negative titers (<10 mIU/ml). Of these, 12 (48%) had HBsAb levels of at least 10 mIU/ml with a

mean of 205.3±129.9 mIU/ml. At seven months after the first vaccination, 8 (32%) had negative HBsAb titers. There were 17 (68%) who had HBsAb levels of at least 10 mIU/ml with a mean of 459± 323.8 mIU/ml.

In this vaccination method, 3 patients complained of pain and erythema at the injection sites 24 hours after the vaccination. None reported body temperatures above 37.5˚C within the following week after the injection.

There were 25 patients randomly chosen to receive the IM vaccination method, 13 males and 12 females who had a mean age of 43.9±13.7 years. All patients survived during the study. At three months after the first vaccination, 9 (36%) had negative titers (<10 mIU/ml). There were 16 (64%) who reached HBsAb levels of at least 10 mIU/ml with a mean of 112.4±96.2 mIU/ml. At seven months after the first vaccination, 8 (32%) had negative HBsAb titers. A total of 17 (68%) had HBsAb titers of at least 10 mIU/ml with a mean of 294.6±277.5 mIU/ml.

No patient complained of pain or erythema at the injection site 24 hours after administration of the vaccine. No patient reported elevations in body temperature above 37.5˚C within the following week.

The mean age of the ID group was 37.48±8.9 years and for the IM group, it was 43.9±13.7 years. According to the student's t-test there was no significant relation between age in the IM and ID groups (p=0.09, t=1.7).

As shown in Table 1, according to the Mann Whitney test there was no significant relation between mean HBsAb titers at the third month for the ID and IM groups (p=0.63). Similarly, there was no significant relation between mean HBsAb titers at seven months after the first injection in the ID and IM groups (p=0.95).

According to the Mann Whitney test, there was no significant relation between number of years of hemodialysis and HBsAb titers in the third and seventh months in both groups (Table 2).

Table 1: Mean±SD of hepatitis B antibody (HBsAb) titers at three and seven months following the first vaccination dose in the intradermal (ID) and intramuscular (IM) groups.

Month	IM Mean ± SD	ID Mean ± SD	*p*-value
Titer 3	112.4±96.2	205.3± 129.9	Z=0.47% p=0.63
Titer 7	294.6±277.5	459±323.8	Z=6% p=0.95

Table 2: Mean±SD hepatitis B antibody (HBsAb) titers in the third and seventh months and duration(years) since the start of hemodialysis.

Group		- (HBsAb < 10 IU/ml)	+ (HBsAb > 10 mIU/ml)	*p*-value
3rd month	ID	1.38±2.75 years	1.24±2.94 years	0.44
	IM	0.98±2.82 years	1.24±3.05years	0.75
7th month	ID	1.12±2.61 years	1.40±3.16 years	0.287
	IM	0.83±2.77 years	1.3±3.14 years	0.477

duration (years), (-) negative for antibody. (+) positive for antibody

DISCUSSION

Due to the generally low response rate to HB vaccine among patients with ESRD, multiple attempts have been made to enhance the immune response to this vaccine. One attempt includes changing the mode of injection from IM to ID(5-7).

The most important factor to prevent the spread of HB in a hemodialysis unit is the application of universal precautions. The CDC also recommends isolating antigen-positive patients and prohibiting the use of shared medications such as heparin vials among dialysis patients(8). Data exist that support the addition of immune stimulants or adjuants (oral levamisole) to improve antibody production against HB(9). The ID method for HB vaccination in healthy individuals has been previously suggested by several authors(10).

The ID method has been used for immunization against rabies and other infections(11). Some authors intradermally administered HB vaccine in uremic patients who had not been previously vaccinated(12). Others used the ID method to vaccinate against HB in individuals who did not seroconvert when vaccinated with the IM method(3).

The results of a study on hemodialysis patients suggested that the ID method was better than the conventional IM method(13). The current case control study intended to verify this suggestion. In the current study, the low dose ID vaccination method showed better results than the IM method. The response rate to recombinant HB vaccine in the IM group was 50% to 60%(14), however in the current study the response rate in the IM and ID groups was 68%. There was no significant relation between HBsAb titers in the third and seventh months in the ID and IM groups. The seroconversion rate of the low dose ID vaccination was 68%.

In a study by Fabrizi et al., the seroconversion rate with 10 µg ID vaccinations in previously unvaccinated hemodialysis patients was 81%(15).

Roozbeh et al. performed a study in Shiraz to compare 20 µg ID versus 40 µg IM vaccinations. The HB vaccination was administered to patients on chronic hemodialysis in three doses given in months 0, 1 and 4.

The seroconversion rate with HBsAb levels of at least 10 mIU/ml was 55.6% (second month) and 50% (sixth month) following the last vaccination in the IM group versus 54.3% (second month) and 50% (sixth month) in the ID group(16). In 2006, Chanchairujira et al. reported that 25 patients were given a total of seven doses of 10 µg Engerix B ID every two weeks whereas 26 patients were given 40 µg IM at months 0, 1, 2 and 6. The seroconversion rate in the third month was 76% and 92% in the seventh month in the ID group; it was 42% (third month) and 65% (seventh month) in the IM group(17). However in the current study, the seroconversion rate with four low dose ID HB vaccinations was 68% (17 out of 25). HBsAb titers in the third month of the ID HB vaccination schedule were higher than the IM group, 205.3±129.9 mIU/ml (ID) versus 112.4±96.2 mIU/ml (IM). In the seventh month of the ID HB vaccination, HBsAb titers were higher in the ID group, 459±323.8 mIU/ml (ID) versus 294.6±277.5 mIU/ml (IM; Fig. 1).

In hemodialysis patients the immune response is generally low. Possibly there are three important factors for seroconversion of HB vaccinations in hemodialysis patients, such as the method of inoculation (ID versus IM), increasing the vaccine dosage (10 µg versus 4 µg), and increasing the number of doses to at least 4, 7 or 10 injections.

In the current study we used four doses of 4 µg Engerix B, administered ID, at months 0, 1, 2 and 6. This schedule gave a seroconversion rate of 40.4% (third month) and 68% (seventh month) after the first vaccination. Some authors noted increased antibody response rates with increased intervals between dialysis and administration of the HB vaccine(18). However, in our study there was no relationship between these two parameters (Table 2). In the current study, the adverse effects of the vaccine included minor pain at the ID injection site in 3 out of 25 patients. In the IM method no patients complained of pain or erythema at the injection site. After one month following the last injection, no patients in either group exhibited any adverse effects such as neurological complications, meningitis or Guillain-Barre syndrome.

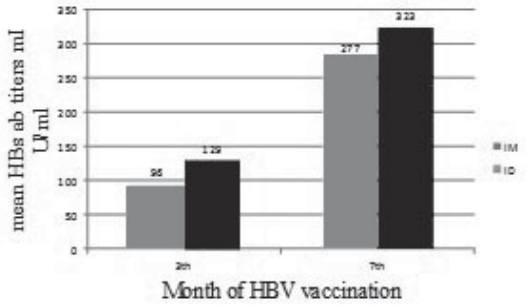

Fig 1.: Mean SD of hepatitis B antibody (HBsAb) for both groups in the third and seven months after the first vaccination.

Although the IM method is easier than the ID method, with training health workers can administer the vaccine by the ID method. However the low cost of the ID method is an important factor.

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