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Full Length Research Paper

The comparison of intradermal versus intramuscular vaccination of hepatitis B in healthcare workers who fail to respond to previous repeated intramuscular vaccines

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Vaccination is recommended for all healthcare workers (HCWs) at risk of exposure to blood and body fluids to prevent occupational acquisition of hepatitis B virus (HBV). However, about 5% of HCWs after 6 doses of intramuscular injections of vaccines fail to develop protective antibody levels (anti HBs). These groups are named non-responder. To compare the humoral immune responses of intramuscular (IM) and intradermal (ID) vaccination in non-responder HCWs, we designed an open, prospective trial. In this trial, we chose HCWs who did not respond to several booster doses of IM hepatitis B vaccine. Three doses of IM or ID recombinant vaccine were injected with two weeks interval in each group. Hepatitis B antibody responses (anti HBs) were assessed one month after last injection. Seroconvertions were observed in 95.5% of ID group and 85% of IM group of these non-responder subjects after vaccinations. ID recombinant hepatitis B vaccination induced protective antibody responses in more than 95.5% of HCWs non-responsive to repeated IM hepatitis B vaccination and can be considered for all non-responder HCWs.

Key words: Vaccination, healthcare workers, nonresponder, hepatitis B virus.

INTRODUCTION

Vaccination is recommended for all healthcare workers (HCWs) at risk of exposure to blood and body fluids to prevent occupational acquisition of hepatitis B virus (HBV) (Playford et al., 2002; Centers for Disease Control and Prevention, 1997; National Health and Medical Research Council, 1997). However, about 12% of HCWs who receive primary intramuscular (IM) vaccination fail to develop protective hepatitis B surface antibody (anti HBs) concentration (≥ 10 mIU/mL) (Roome et al., 1993; Wood et al., 1993) and remain at risk for occupationally acquired HBV infection (Playford et al., 2002; Szmuness et al., 1980).

Some risk factors for vaccine non response include male gender, older age, cigarette smoking (Roome et al.,1993; Wood et al., 1993; Yen et al., 2005), renal failure (Stevens et al., 1984), chronic liver disease (Aziz et al., 2006), intragluteal vaccine administration (Lindsay et al., 1985; Chen and Gluud, 2005, 2008), certain human leukocyte antigen (HLA) haplotype (Alper et al., 1989; McDermott et al., 1998), and height and weight (body mass index) (Playford et al., 2002; Weissman et al., 1988).

Current guidelines (Centers for Disease Control and Prevention, 1997; National Health and Medical Research Council, 1997) for management of HCWs who fail to respond to primary IM vaccination recommend additional

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Table 1. Characteristics of study subjects.

Subject	Gender	Age (years)	BMI (kg/m^2)[1]	No of prior boosters[2]	Time since last dose (years)	Vaccination route	Anti HBs levels after vaccination	Smoking (P/Y)[3]
1	F	50	41.4	9	1	ID	200*	0
2	F	41	21.0	7	10	IM	200*	0
3	F	50	16.4	6	2	ID	179	0
4	F	33	15.2	6	6	ID	200*	0
5	F	49	20.3	6	2	ID	200*	0
6	F	33	21.2	6	5	ID	200*	0
7	F	48	24.9	6	5	ID	200*	0
8	F	50	19.7	6	5	ID	92	0
9	F	38	17.9	6	3	ID	200*	0
10	F	36	15.6	6	2	ID	4	0
11	F	35	17.6	6	3	ID	200*	0
12	F	25	18.2	6	0.8	ID	200*	0
13	F	50	24.2	6	2	ID	200*	0
14	F	40	15.8	6	1	ID	9	0
15	F	46	22.4	6	6	ID	70	0
16	F	41	33.2	6	2	ID	88	0
17	F	47	17.8	5	15	ID	150	0
18	F	41	18.1	5	10	ID	73	0
19	F	34	23.4	5	2	ID	172	0
20	F	38	20.8	5	7	ID	200*	0
21	F	50	18.7	4	5	ID	200	0
22	F	32	19.6	4	3	ID	44	0
23	F	30	17.0	4	0.6	ID	125	0
24	F	28	19.5	4	1	ID	40	0
25	F	42	19.4	4	2	ID	19	0
26	F	46	18.6	3	2	ID	28	0
27	F	38	17.5	3	10	ID	170	0
28	F	27	16.4	3	1	ID	200*	0
29	M	51	21.6	6	8	ID	200*	0
30	M	52	27.4	6	3	ID	200*	0
31	M	35	19.7	6	1	ID	150	0
32	M	49	18.2	6	2	ID	38	0
33	M	42	21.1	6	1	ID	200*	0
34	M	41	26.7	6	1	ID	200*	0
35	M	32	20.4	6	3	ID	200*	0
36	M	40	19.3	6	2	ID	181	20
37	M	52	22.9	6	1	ID	76	7
38	M	56	14.3	6	10	ID	131	5
39	M	48	22.8	5	2	ID	200*	0
40	M	57	19.7	5	2	ID	46	0
41	M	25	20.2	4	3	ID	118	0
42	M	38	25.7	4	2	ID	200*	0
43	M	53	23.2	4	3	ID	200*	0
44	M	46	25.0	3	2	ID	200*	25
45	F	23	15.1	7	3	ID	200*	0
46	F	23	18.0	6	4	IM	200*	0
47	F	34	16.3	6	1	IM	9	0
48	F	33	19.4	6	7	IM	80	0
49	F	46	19.5	6	1	IM	200*	0

Table 1. Contd.

50	F	46	19.3	6	6	IM	100	0
51	F	26	15.8	6	5	IM	86	0
52	F	47	25.0	6	1	IM	200*	0
53	F	49	21.5	6	8	IM	86	0
54	F	48	19.8	5	2	IM	125	0
55	F	38	24.1	5	3	IM	200*	0
56	F	44	27.3	5	1	IM	46	0
57	F	32	15.0	5	2	IM	161	0
58	F	49	22.7	4	1	IM	66	0
59	F	22	20.3	4	4	IM	200*	0
60	M	42	22.2	6	1	IM	0	0
61	M	37	22.4	5	5	IM	200*	0
62	M	30	23.0	4	5	IM	200*	0
63	M	34	24.0	3	1	IM	4	1
64	M	30	25.6	3	4	IM	44	1

[1]Body mass index, [2]number of booster vaccine doses in addition to three primary vaccine doses, [3]pack years, * ≥ 200 mIU/ml.

IM doses (booster doses), although response rate are gene-rally less than 50% (Alper et al., 1989; McDermott et al., 1998; Weissman et al., 1988; Struve et al., 1994; Chen and Gluud, 2008). In contrast, response rate of about 90% have been reported with ID hepatitis B vaccine using either recombinant (Playford et al., 2002; Levits et al., 1995) or plasma-derived vaccine (Nagafuchi et al., 1991).

We design this study for further assessing the humoral immune responses, safety and tolerability of ID re-combinant hepatitis B vaccination and comparing with IM vaccination in HCWs non-responsive to repeated IM vaccination.

MATERIALS AND METHODS

All HCWs in three hospitals in Tehran were assessed (cluster sampling). Any HCWs who have no protective anti HBs levels (≥ 10 mIU/ml) were chosen. Inclusion criteria for this study were HCWs who had:

1. Previously received a primary of at least 3 booster doses (equal to at least 6 doses) of hepatitis B vaccine;
2. Failed to respond to vaccines as documented by appropriately timed post vaccination serology;
3. Received all previous vaccine doses IM into the deltoid muscle;
4. Not received a vaccine dose within the previous 6 months;
5. Negative baseline hepatitis B core antibody (anti HBc) and hepatitis B surface antigen (HBs Ag);
6. Anti HBs levels of less than 10 mIU/ml;
7. No history or laboratory evidence of immunodeficiency, renal failure or hepatic dysfunction.

Subjects were divided randomly in two groups and then vaccinated either with ID or IM route. There was no statistical difference be-tween the two groups in variables such as gender, age, body mass index (BMI), number of previous injections, time from last injection and smoking.

The used vaccines were Hepavax-Gen, a Korean recombinant hepatitis B vaccine, and all subjects were injected by one physician. Intradermal group subjects were vaccinated with 5 microgram (0.25 ml) and a 1 ml insulin syringe (29-gauge needle) to the arm, and intramuscular group subjects were vaccinated with 20 microgram (1 ml) and a 2 ml syringe (22-gauge needle). A total of 3 doses were given every second week to both groups. Direct questioning of subjects and inspection of the injection site 48 to 72 h after each dose was done to detect local reactions, tenderness and other side effects such as fever.

A total of 134 HCWs were included in our trial, sixty five in ID group and sixty nine in IM group. Sixty four subjects (43 women and 21 men) finished our trial (Table 1). In final participants, the median age were 41 (range 22 to 57) years. The median BMI were 20.01; (range 14.29 to 41.38) kg/m^2). 4.7% of subjects had BMI more than 30.1 kg/m^2. 6 (9.4%) were current cigarette smokers. Subjects had received previously between 3 to 9 IM injections of boosters of hepatitis B vaccines (mean 6 doses). The mean range of last injections was 3.5 (0.6 to 15) years. HLA patterns were not included in our study. Concentrations of anti HBs were determined at baseline and one month after last vaccine dose by Enzyme-linked immunosorbent assay (ELISA) method. Levels of 200 mIU/ml or greater were not further quantified; these were treated as equal to 200 mIU/ml for calculations of mean antibody concentration. Sta-tistical analysis was done between two groups by independent sample t-test.

RESULTS

All of the subjects received 3 doses of vaccine, 44 (68.2%) intradermal and 20 (31.8%) intramuscular. In ID group subjects, 22 (50%) had concentration of anti HBs more than 200 mIU/ml, 9 (20.5%) between 100 to 199 mIU/ml, 11 (25%) between 10 to 99 mIU/ml, 2 (4.5%) below 10 mIU/ml and total mean antibody level of 145.5 mIU/ml (Tables 2 and 3). In IM group subjects, 8 (40%) had concentration of anti HBs more than 200 mIU/ml, 3 (15%) between 100 to 199 mIU/ml, 6 (30%) between 10

Table 2. Separative antibody response in the study subjects.

Subjects group \ Antibody response		<10	10-99	100-199	≥200	Total
Intradermal	Female	2	8	5	13	28
	Male	0	3	4	9	16
	Total	2	11	9	22	44
Intramuscular	Female	1	5	3	6	15
	Male	2	1	0	2	5
	Total	3	6	3	8	20

Table 3. Antibody levels after vaccination.

Parameter	N	Valid	44
		Missing	0
Intra dermal	Mean		145.52
	Median		190.50
	Mode		200
	Standard deviation		68.838
	Variance		4738.720
	Range		196
	Minimum		4
	Maximum		200
	N	Valid	20
		Missing	0
Intra muscular	Mean		120.35
	Median		112.50
	Mode		200
	Standard deviation		76.626
	Variance		5871.608
	Range		200
	Minimum		0
	Maximum		200

to 99 mIU/ml, 3 (15%) below 10 mIU/ml and total mean antibody levels of 120.3 mIU/ml (Tables 2 and 3). In summary, 42 (95.5%) of ID subjects and 17 (85%) of IM subjects had anti HBs levels of more than 10, a protective level against hepatitis B. No statistical differences were observed between two groups by independent sample t-test analysis (P value = 0.46). Intradermal vaccination was generally well tolerated. Most of the responding subjects had skin reactions at the vaccine site. One subject had a local reaction of about 15 mm after third injections that subsided with local care. Non responding subjects had no such reactions. No other complications were seen.

DISCUSSION

In this study, 42 of 44 (95.5%) subjects had protective anti HBS Ab levels following ID vaccinations. These HCWs were previously considered unlikely ever to respond to hepatitis B vaccination, all having failed to seroconvert, despite repeated previous intramuscular vaccine doses and must be considered as nonresponder and having risk factors associated with non response.

Primary ID hepatitis B vaccination has been associated with poorer seroconvertion rates and lowers anti HBs levels than IM vaccination (Center for Disease Control and Prevention, 1991), possibly reflecting lower vaccine doses (2 µg versus 5 µg), inadvertent subcutaneous vaccine administration, or both. Similar to others (Playford et al., 2002; Nagafuchi et al., 1991), in this study we sought to optimize vaccine responsiveness by using higher vaccine doses and one physician ex-perienced in administering ID injections. The antibody responses elicited by ID route in this study were high: half of the subjects had maximum responses more than 200 mIU/ml and 95.5% of subjects had responses more than lower limits of protective antibody. These concentrations are higher than those of other studies of ID vaccination of HCWs nonresponsive to intramuscular vaccination (Levits et al., 1995; Nagafuchi et al., 1991).

We also compare ID route with IM route for better evaluation of ID route. Although no statistically significant differences exist between two groups of ID and IM subjects, but a response rate of 95.5% with mean increase of 145.5 mIU/m in HCWs who did not respond to any previous IM injections was very significant. Two reasons of this problem are: first, low sample size and second the IM group subjects received vaccine with two weeks interval, same as ID group, which is not a recommended schedule (0, 1 and 6 months) (Chen and Gluud, 2008). This means that our control group probably was not a true control.

The duration of protection from HBV infection conferred by intradermal vaccination is uncertain. It is currently believed that prolonged protection from clinically significant infection independent of subsequent waning antibody concentrations is conferred to individuals who have an initial protective response to intramuscular vaccination. We would expect that HCWs who respond to ID vaccination should also experience prolonged protection (Playford et al., 2002; Chen and Gluud, 2008; West and Calandra, 1996; Assad and Francis, 1999), despite the lower peak

antibody responses elicited by ID vaccination (Bryan et al., 1992).

Playford et al. (2002) reported that more than 90% of previously non-responsive HCWs responded to ID recombinant hepatitis B vaccine with protective anti HBs levels without comparison with control group, and to our knowledge, we did not find any published study in this regard. So, on the basis of our results, we recommend that non-responder HCWs receive three ID vaccine doses followed by assessment of anti HBs levels. For persistent non-responders, it is unclear whether additional doses would induce seroconvertion.

We have demonstrated that ID recombinant hepatitis B vaccination induced protective antibody responses in more than 95.5% of HCWs nonresponsive to recommended IM hepatitis B vaccination. Also, IM recombinant hepatitis B vaccination with two weeks interval induced protective antibody level of about 85% of such subjects. These vaccinations are safe and well tolerated, and thus can be considered for all nonresponder HCWs.

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