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## Intradermal hepatitis B virus vaccination for low- or non-responded health-care workers.

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## Abstract

Immune responses to hepatitis B virus (HBV) vaccine in six low- or non-responded health-care workers were tested with an intradermal low dose (5 micrograms) of the recombinant vaccine. The injection was repeated three or four times at fortnightly intervals. These successive doses of the vaccine induced a high concentration of antibodies with delayed-type hypersensitivity (DTH) skin reactions in all six subjects. A few minor temporary side effects, such as irritation and itching at the injection site, were reported by some of the vaccinees. The results suggest low-dose of intradermal HBV vaccinations for low- or non-responders are safe and readily effective.

**KEYWORDS:** skin reaction, recombinant HBV vaccine

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## Intradermal Hepatitis B Virus Vaccination for Low- or Non-Responded Health-Care Workers

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Immune responses to hepatitis B virus (HBV) vaccine in six low- or non-responded health-care workers were tested with an intradermal low dose ( $5\mu\text{g}$ ) of the recombinant vaccine. The injection was repeated three or four times at fortnightly intervals. These successive doses of the vaccine induced a high concentration of antibodies with delayed-type hypersensitivity (DTH) skin reactions in all six subjects. A few minor temporary side effects, such as irritation and itching at the injection site, were reported by some of the vaccinees. The results suggest low-dose of intradermal HBV vaccinations for low- or non-responders are safe and readily effective.

**Key words :** skin reaction, recombinant HBV vaccine

Although the intramuscular HBV vaccination has been shown to be highly effective and readily available for clinical applications in recent years, there are several problems associated with its use; expense, a long antibody-induction period and a relatively high percentage of non-responders (1-3). Unresponsiveness is a serious problem, especially for health-care workers who have a high risk of HBV infection from hepatitis patients and subsequently need to be protected from this occupational hazard (4).

There have been some reports that intradermal vaccination is more immunogenic, requires a lower dose of inoculation, and is thus cheaper than the same vaccine given intramuscularly (5, 6). Intradermal inoculation is also effective for patients with an impaired immune response (7).

The intent of this study was to assess the effectiveness of low-dose intradermal vaccinations for health-care workers who could not obtain detectable anti-HBs antibody response measured by passive hemmagglutination (PHA) test after several routine trials intramuscularly and/or subcutaneously.

Six healthy adult medical staff members (4 males and 2 females; ranging from 27 to 57 years old, with a mean of age 38 years old), who were unable to acquire a protective anti-hepatitis B surface antibody (anti-HBs) level after several previous inoculations using the routine intramuscular or subcutaneous administration of the recombinant HBV vaccine, were selected for this study. Before the present vaccination, all subjects were determined to be hepatitis B surface antigen (HBsAg), anti-hepatitis B core (anti-HBc) antibody negative as measured by radioim-

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munoassay, and had normal aminotransferase levels.

Vaccinees received three intracutaneous injections of the yeast-derived recombinant HBV vaccine (Bimmugen; 20  $\mu$ g of purified HBsAg in 1 ml, Fujisawa Pharmaceutical Co., Tokyo, Japan) every two weeks as reported by Nagafuchi *et al.* (8). The average interval between the last conventional vaccination and the first intradermal injection was one year (range, 6 months–2 years). On each occasion, a dose of 5  $\mu$ g (0.25 ml) was given intradermally in the upper shoulder to conceal the injection site (8). One month after the third dose, serum levels of anti-HBs were measured by PHA test in each vaccinees.

Delayed-type hypersensitivity (DTH) skin reaction was evaluated 48 h after intradermal injection by measuring the diameter of erythematous change and/or swelling of the skin. In this skin reaction, subjects were judged to be positive if the diameter of either skin response was 3 mm or more (9).

The table shows the seroconversion of the subjects injected in the present study. Two weeks after the third injection, 5 out of 6 vaccinees had detectable anti-HBs. Although Case 2 was negative at this point, she developed antibodies three weeks after the fourth inoculation (6 weeks). The

detected anti-HBs levels ranged from  $2^2$  to more than  $2^6$  and were thus high enough to be protective.

The table discloses the DTH reactions following the intradermal HBV vaccination. These skin reactions were detected in all responders and occurred on average 2.0 weeks after the first injection.

There was no systemic side effect, skin ulceration or granuloma. On the day of injection, four cases complained the irritation and itching at the injection site. The skin eruption was observed two days after the 2nd vaccination in Case 5. The lesion showed redness (2 cm in diameter) and subsided after several weeks, leaving a small pigmented macula in one case.

In the present study, we examined the effect of intradermal vaccination of HBsAg on the anti-HBs antibody production in persons who had not acquired anti-HBs by several previous trials for more than two years. They were medical staff, constantly exposed to the danger of HBV, and all of them were able to develop anti-HBs production after three or four times of intradermal vaccination. Seroconversion rates after intramuscular or subcutaneous re-vaccination have been reported to be low (10). Therefore, these data indicate that intradermal vaccination can be an

**Table.** Skin reactions and anti-HBs levels after an intradermal vaccination series with a yeast-derived recombinant HBV vaccine

No.	Age (Years)	Sex	Past history of HB vaccination (Series)	Skin reaction induction period after the first vaccination <sup>a</sup> (Weeks)	Anti-HBs after the first vaccination <sup>b</sup>	
					5 weeks	9 weeks
1	29	M	3	0	> 2 <sup>5</sup>	N.T. <sup>d</sup>
2	27	F	4	6	— <sup>c</sup>	2 <sup>3</sup>
3	57	M	5	2	2 <sup>4</sup>	N.T.
4	37	M	5	2	> 2 <sup>6</sup>	N.T.
5	48	F	5	0	2 <sup>6</sup>	N.T.
6	30	M	4	2	2 <sup>6</sup>	N.T.

*a* : Delayed type hypersensitivity (DTH) skin reactions were evaluated 48 h later after intradermal injection by measuring the diameter of erythematous change and/or swelling of the skin. Subjects were judged to be positive when the diameter of either skin response was 3 mm or more.

*b* : The passive hemagglutination test was used to detect anti-HBs.

*c* : not detected.

*d* : N.T., not tested.

alternative method to induce anti-HBs in those categorized as low- or non-responders after repeated conventional vaccinations. Further, most recipients acquired anti-HBs within five weeks after intradermal re-vaccination, suggesting that intradermal vaccination is also effective in accelerating the immune response in persons who were unexpectedly exposed to HBV-positive, especially HBeAg-positive sera.

We used  $5\mu\text{g}$  of recombinant HBsAg for intradermal vaccination as reported by Nagafuchi *et al.* (8). Although  $10\mu\text{g}$  of recombinant HBsAg is usually used in conventional vaccination, lower dose of HBsAg was enough to induce antibody response even in persons who were judged to be low- or non-responders. The high cost of plasma-derived or recombinant HBV vaccine is a serious economic obstacle to the extensive immunization against HBV. Our present data suggest the possibility of reducing the amount of antigens required for immunization by using the intradermal route.

The mechanism by which intradermal vaccination can stimulate antibody response more effectively than intramuscular or subcutaneous route remains uncertain. Intradermal inoculation of antigen has been reported to be effective even for the patients with Down's syndrome, who usually have an impaired immune response (7). Our study showed that positive skin test preceded the anti-HBs production in each recipient, suggesting that development of DTH might represent the acquisition of a cellular immune response to HBsAg (11, 12). The presentation of HBsAg to the immune system intradermally may result in an effective macrophage-dependent T-lymphocyte response via specific epidermal cells (13).

Although long-term efficacy of intradermal vaccination for anti-HBs production needs to be determined, it has several advantages as shown in this study. This method should be considered for health-care workers who responded poorly to HBV vaccine administered routinely.

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