

Immunogenicity of Low Dose Intradermal Hepatitis B Vaccine and its Comparison with Standard Dose Intramuscular Vaccination

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A prospective study was carried out in the well baby and immunization clinics of tertiary care hospital to compare the immunogenicity of low dose hepatitis B vaccine (HBV) given intradermally versus standard dose given intramuscularly. One hundred ninety six term, healthy, Australia antigen negative and exclusively breast fed babies were allocated into two groups in a simple randomized manner. In group I, hepatitis B vaccine was given in low dose (2 µg) by intradermal route whereas in group II it was administered in standard dose (10 µg) by intramuscular route. Diphtheria, pertussis, tetanus (DPT) and oral polio vaccine (OPV) were co-administered with HBV in both the groups at 6, 10 and 14 weeks of age at different sites. One hundred seventy seven infants could be regularly followed up and tested for anti-HBs titres by third generation ELISA test using mono-ELISA anti-HBs 3.0 kits. Geometric mean titres of anti-HBs were estimated in each group and compared. Student's t-test was used for statistical analysis. Seroprotective anti-HBs titres (titre > 10 mIU/mL) were achieved in 87/88 (98.8%) children having received intramuscular doses as compared to 82/89 (92.1%) children in the intradermal group. The geometric mean titres of the intradermal group were 92.71 mIU/mL (95% C.I. 68.85-124.85), significantly lower than 331.66 mIU/mL (95% C.I. 245.12-448.78), noticed in the intramuscular group. There were no significant adverse reactions in both the groups. Hepatitis B vaccine is immunogenic when co-administered with DPT and OPV vaccine. The intradermal hepatitis B administration is less effective with lower immunogenicity than the intramuscular vaccination.

Key words: Hepatitis B vaccine, Immunogenicity, Intradermal, Intramuscular.

Hepatitis B Virus (HBV) infection, a silent killer is the major cause of morbidity and mortality. It is a serious global health hazard with three quarters of world's population living in areas where prevalence of HBV infection is 2% or more. About 400 million individuals are chronic carriers globally and some 43 millions HBV carriers occur in India which is the second largest pool of carriers after China(1). Two third cases of chronic liver disease and hepatocellular carcinoma in India are due to HBV infection. The simple way to guard against this dreadful disease is by vaccination(2). The widely accepted schedule of administering 10

µg of hepatitis B vaccine at 0, 1 and 6 months has been used(3). In order to improve compliance of vaccinees, strategies to administer the vaccine along with the EPI contacts have been carried out(4-6). The other important aspect to further improve the compliance is by reducing the immunizing dose via intradermal administration and hence the cost of the vaccine. The immunogenicity of this strategy has not been widely studied in pediatric population(7-9). The present study was carried out to find out the immunogenicity of low dose intradermal hepatitis B vaccine and to compare its efficacy with intramuscular vaccination.

Subjects and Methods

One hundred ninety six infants born at term were enrolled in the present study at 6 weeks of age. Out of which one hundred seventy seven infants could be regularly followed up 4 weekly till 18 weeks of age. The anthropometric indices (weight, head circumference, chest circumference and crown heel length) along with the clinical examination was carried out in each child. The study material comprised of healthy, Australia antigen negative and exclusively breastfed babies. All the babies were allocated to two groups in a simple random manner.

Groups

Group I: (n = 89) Hepatitis B vaccine (2 µg) was administered into the volar aspect of forearm intradermally.

Group II: (n = 88) Hepatitis B vaccine (10 µg) was administered by intramuscular route into the antero-lateral part of thigh.

The hepatitis B vaccine was co-administered with DPT & OPV vaccines at 6 weeks, 10 weeks and 14 weeks. The vaccines were given at different sites.

The informed consent was taken from the parents of studied children and the protocol was approved by the ethical committee of the institution.

The antibody titres on children in both the groups (Anti HBs) were measured after 4 weeks of the last dose *i.e.*, at 18 weeks by immunoenzymatic method using monoelisa anti HBs 3.0 kits. Quantitative values of anti HBs were obtained from the standard curve constructed using known standards. Geometric mean titres (GMT) and confidence intervals were calculated by logarithmic transformation of data. GMT of >10 mIU/mL was considered seroprotective(9). The third generation ELISA

test was used for determination of HbsAg status of infants. Student's t-test was used to find out statistical significance of anti HBs titres in the two groups.

Results

One hundred seventy seven infants out of a total of 196 infants could be regularly followed up. Thus the compliance rate was 90.3%. There was no statistical difference in both groups in terms of sex, weight distribution and other anthropometric indices (*Table I*).

The seroprotective rate (Anti HBs >10 mIU/mL) among 89 subjects in group I was noted in 92.1% of cases with a geometric mean titres of 92.71 mIU/mL. Similarly in group II the seroprotection rate was 98.8% with attainment of 331.66 mIU/mL of geometric mean titres of anti HBs (*Table II*).

The titre obtained in intradermal group though higher than the recommended seroprotective value was significantly lower than that obtained in the intramuscular group. Regarding the adverse effects during the course of vaccination, 4 cases developed erythema at the injection site in group I whereas no untoward effects were observed in group II.

Discussion

The present study was undertaken with the aim of evaluating the efficacy of intradermal hepatitis B vaccine as few studies from India(10-13) and abroad(14-18) found it to be an effective route of vaccination. The other objective was to compare the immunogenicity of intradermal *vs.* intramuscular routes, keeping the host factors similar to minimize the confounding variables of immunogenicity. The attainment of high titres above the seroprotective levels in the intradermal group prove it to be an effective mode of administration however the titres were significantly lower than that attained in the

TABLE I—Demographic Characteristics of Studied Groups.

Variable	Group I n = 89	Group II n = 88	p-value
Sex: Male	60	58	0.83
Female	29	30	
Weight (kg)	4.16 ± 0.53	4.08 ± 0.61	0.35
Head circumference (cm)	36.89 ± 0.89	37.09 ± 1.22	0.21
Chest circumference (cm)	35.59 ± 0.99	35.89 ± 1.29	0.84
Crown-heel length (cm)	54.58 ± 1.43	54.74 ± 1.89	0.53

TABLE II—Comparative Immunogenicity of Low Dose Intradermal vs Standard Dose Intramuscular Hepatitis B Vaccination.

Variable	Group I (Intradermal group) (n = 89)	Group II (Intramuscular group) (n = 88)	p-value
Mean Anti -HBs titres (mIU/mL)	208.26 ± 345.58	692.27 ± 675.44	<0.001
Seroprotective rate (>10 mIU/ mL)	92.1%	98.8%	<0.05
Geometric mean titres (GMT) mIU/mL (95% C.I.)	92.71 (68.85-124.85)	331.66 (245.12-448.78)	<0.001

intramuscular group. The concept of intradermal inoculation of vaccines originated from observations of Thompson, *et al.* (19) who stated that modified epidermal cells (Langerhans cells) present in dermis are antigen representing cells.

The lower antibody titres need to be followed up for a prolonged period of time to ascertain its seroprotective efficacy, however this issue could not be addressed by the present study. There are not many studies in the pediatric age group globally and to the best of our knowledge no Indian study is available in literature on intradermal hepatitis B vaccination in children. The study conducted by Coberly, *et al.* (7) on 75 healthy infants having received 2 µg of intradermal hepatitis B vaccine at 0, 2 and 4 months of age showed a

seroprotection rate of 92%. The geometric mean titre of anti HBs attained in the study was 312 mIU/mL. The variation in the accomplishment of titres from the present study could be due to adoption of different, vaccination schedule and/or ethnic differences in the two studied groups. To conclude, the intradermal route is less effective with lower immunogenicity than the intramuscular route, therefore intradermal route is not the preferred route for hepatitis B vaccine.

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Key Messages

- Hepatitis B vaccine is immunogenic when co-administered with DPT and OPV vaccine.
- Intradermal and intramuscular routes are effective ways of administration of hepatitis B vaccine.
- Intradermal vaccination of hepatitis B is less effective with lower immunogenicity than intramuscular vaccination.

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