Comparison of intradermal and intramuscular administration of hepatitis B vaccine in neonates

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Background: Hepatitis B virus (HBV) infection and its complications are among the most common diseases in Iran. National mass vaccination of neonates against hepatitis B was started in 1991, but was considered a costly venture. Aim: To compare the efficacy of low-dose intradermal HBV recombinant vaccine with standard intramuscular dose in neonates. Method: 165 apparently healthy neonates born in Shiraz were randomized to receive either 10 mcg of recombinant vaccine intramuscularly (IM; n=82) or 2 mcg vaccine intradermally (ID; n=83) at months 0, 1, 6. Anti-HBs titers were measured at 6 and 18 months after the first dose. Results: 53 and 51 neonates in the IM and ID groups, respectively, completed the study. Protective anti-HBs titers (>10 IU/L) at 18 months after the first dose were achieved in 98.1% and 96.2% of neonates in IM and ID groups, respectively (p=ns). The only side effect in the ID group was local hyperpigmentation, which was seen in 55%; no significant side effect was reported in the IM group. Conclusion: Intradermal vaccination with 20% of standard dose is as effective as IM vaccination when evaluated at 18 months after the first dose. [Indian J Gastroenterol 2001;20:94-96]

Key words: Hepatitis B vaccination

Universal neonatal vaccination has been shown to be the most effective way to control hepatitis B virus (HBV) infection. Since 1991, this has been introduced in the national Iranian children vaccination program and all neonates receive this vaccine intramuscularly (IM) in the first week of life and at one and 6 months, free of charge. The vaccine is imported and costly and has a major adverse impact on the health budget. It has been shown previously that intradermal (ID) vaccination with reduced dosage may have the same immunogenicity as the standard intramuscular dose in healthy adults. This randomized, controlled trial was undertaken to find out whether this route of vaccination is effective in neonates.

Methods

Apparantly healthy full-term neonates (n=165; 94 males) referred to a health center in Shiraz, Iran in the first week of life for routine vaccination were included in the study. All neonates were examined and history was obtained from their parents. A questionnaire about age of mother, her socioeconomic and health status, mode of feeding and child's birth weight was filled. Children with history of liver disease in first-degree relatives, apparent congenital anomalies on physical examination, and those with acute febrile illness were excluded. Included neonates were alternately assigned to receive a recombinant vaccine (Heberbiovac HB; Heberlitech, S.A. Havana, Cuba) either as 10 mcg intramuscularly or as 2 mcg intradermally. Information about the study design was explained to the parents and informed consent was taken. The protocol was approved by the research committee in the Ministry of Health and Medical Education.

Intramuscular injections were given in the quadriceps muscles anteriorly. Intradermal injections were given on the lateral aspect of the arm. Other vaccines including BCG were given as scheduled. Vaccination was repeated at 1 and 6 mo of age with the same dose and the same mode in each group. At 6 mo of age, upon injection of the 3rd dose of vaccine, serum samples were obtained from neonates and their mothers and tested for anti-HBs (Biostest, Germany) and HBsAg (ELISA; Biostest, Germany), respectively. Also, at 18 mo of age, serum samples were obtained from participating neonates and tested for anti-HBs. At each visit, parents were questioned about any side effect of vaccination and neonates were examined with special attention to the site of vaccine injection.

Data were analyzed with SPSS software using $c^2$ test, Student's $t$ test and Fisher's exact test, as appropriate. P value lower than 0.05 was considered significant.

Results

Of the 165 neonates, 82 were randomized to receive ID vaccine and 83 to IM vaccine. The characteristics of the two groups are shown in Table 1.

Result of anti-HBs titers at 6 mo and 18 mo of age are shown in Table 2.

Geometric mean titer of anti-HBs at 6 mo of age was 54.0 IU/L in the IM group and 73.7 IU/L in the IM group. At 18 mo of age, only 51 in the ID group and 53 in the IM group returned for follow up. Geometric mean anti-HBs titer was 81.9 IU/L and 90.2 IU/L at 18 mo in the ID and IM groups, respectively. No relation was found between birth weight, gender, mother's age, parent's
level of education, family's socioeconomic status, type of infant's feeding and anti-HBs titer. No mother was HBsAg-positive upon the third dose of the infant's vaccination.

No systemic side effect was reported in any neonate after vaccination. Local hyperpigmentation occurred in 45 (55%) neonates in the ID group, whereas one (1%) infant developed local hypopigmentation at the site of injection when examined at 6 mo. No side effect was reported in the IM group.

Discussion

There has been a controversy about the efficacy of low-dose ID vaccination against hepatitis B as compared to the IM route. While some authors reported unsatisfactory antibody response, others found a similar antibody response in healthy adults. Infants, pre-school children, and even mentally retarded patients have been reported on ID administration were not in neonates and did not have adequate follow-up data. Two of these studies were in neonates. Coberly and colleagues from Baltimore, USA compared these two routes in neonates, with a 6-month follow up. They found that infants in the ID group were less likely to develop protective antibody. A similar trial from Gambi also showed failure of intradermal route using 1 mg doses of vaccine. It appears that the first trial had a shorter follow-up period and the second had used an inadequate amount of vaccine. Our study does not have these shortcomings.

Table 2: Anti-HBs antibody titers (IU/L) at 6 mo and 18 mo of age

<table>
<thead>
<tr>
<th>Titers</th>
<th>Intradermal (n=82)</th>
<th>Intramuscular (n=83)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10</td>
<td>15 (18.3%)</td>
<td>6 (7.2%)</td>
<td></td>
</tr>
<tr>
<td>10-99</td>
<td>41 (50%)</td>
<td>33 (39.8%)</td>
<td></td>
</tr>
<tr>
<td>≥100</td>
<td>26 (31.7%)</td>
<td>44 (53.5%)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>18 months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10</td>
<td>2 (2.5%)</td>
<td>1 (1.9%)</td>
<td></td>
</tr>
<tr>
<td>10-99</td>
<td>16 (19.5%)</td>
<td>12 (22.6%)</td>
<td></td>
</tr>
<tr>
<td>≥100</td>
<td>33 (40.7%)</td>
<td>40 (75.5%)</td>
<td>ns</td>
</tr>
</tbody>
</table>

Although in our study initial antibody response in the ID group was significantly lower than that in the IM group, this difference was abolished when follow up was extended to 18 months. This suggests that with ID vaccination, the peak antibody rise may be more gradual. However, since a large number of neonates developed anti-HBs titer of >10 IU/L, this lower titer may not be clinically significant. Wahl and Hermodsson suggested that correct intradermal deposition of vaccine may be crucial for an adequate immune response.

Some studies have shown better antibody response in women to ID vaccine as compared to IM route, others did not find such a difference. We did not find any difference in antibody response between the genders, with no relation to birth weight, mother's age, level of education in parents and their economic state, and type of feeding.

The most commonly reported side effect of intradermal HBV vaccination has been local, including hyperpigmentation at the site of injection. We also found local hyperpigmentation as the most common side effect of ID vaccine.

Intradermal vaccination, in the schedule that we have used, can reduce the cost of HBV vaccination by 80%. We therefore recommend routine ID vaccination against HBV in Iran.

References


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NEWS AND NOTICES

A Workshop and Continuing Surgical Education Program on Benign Anorectal Anomalies will be held in Pondicherry July 21 - 22, 2001.

For details, contact: Dr K P Singh, Convener, 33 HIG House, Ashok Nagar, Pondicherry 605 008
Tel: (413) 33 8105 (O); 25 1966, 25 0667 (R); 98430 31966

The 14th World Conference of the International Society for Laser Surgery and Medicine will be held in Chennai August 27 - 30, 2001.

For details, contact: Dr B Krishna Rau, President, No. 5 Chandra Bagh Avenue, Second Street, Mylapore, Chennai 600 004
Tel: (44) 859 4804, 852 7776, 476 5856
Fax: (44) 859 4578, 476 7008
E-mail: bkr@vsnl.com
Website: http://www.medindia.net/islam2001

The 9th Asian Conference on Diarrheal Diseases and Nutrition will be held in New Delhi September 28 - 30, 2001.

For details, contact: Prof M K Bhan, Conference Secretary, ASCOD2001, Room No. 3054, Academic Block, Department of Pediatrics, All India Institute of Medical Sciences, Ansari Nagar, New Delhi 110 029
Tel: (11) 696 3822, 659 4792, 656 1123, 656 0110 Ext 3290
Fax: (11) 686 2663
E-mail: ascod2001@delhi.as
Website: http://www.ascodd2001.delhi.as

The 42nd Annual Conference of the Indian Society of Gastroenterology and associated societies will be held in Lucknow November 23 - 29, 2001.

The program includes two pre-conference symposia (on gastrointestinal motility and scientific communication), a postgraduate course / CME, and endoscopy workshop. For details, contact: Prof S R Nalik, Department of Gastroenterology, SGPGI, Lucknow 226 014
Tel: (522) 44 0700, 44 0800 Ext 2400
Fax: (522) 44 0078, 44 0017
Website: http://www.sgpgi.ac.in/conf/isg2001.html