Waning Immunity to Plasma-derived Hepatitis B Vaccine and the Need for Boosters 15 Years After Neonatal Vaccination

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Introduction

- Taiwan started a national program of HB vaccination since 1984.
- A significant reduction of HB carrier rate in children under 10 years from 9.8% to 1.3%.
- Decreased the incidence of HCC in children aged 6 to 9 from 0.52 to 0.13 per 100,000.
The protective levels of Anti-HBs (> 10mIU/mL) can be detected in the great majority (83%-99%) in the vaccinees.

HB vaccine is a subunit protein vaccine, which contains only HBsAg, a limited duration of protection is anticipated.

The proportions of vaccinees with protective anti-HBs levels decreased to 75% to 87% 5 years after vaccination and further drops to 50% to 70% 10 to 12 years after vaccination.

Booster?
Patients and Methods

- Group A: 78 15 year-old adolescents who were born to HBeAg(+) and HBsAg(+) mothers.
- They were documented to have received 4 doses of plasma-derived (5 µg/dose) HB vaccine (Hevac B; Pasteur, Paris, France) at 0, 1, 2, and 12 months during 1988.
- All of them also received 0.5 mL of hepatitis B immunoglobulin (Hyper-Hep, Miles, PA) within 24 hours after birth.
- All were shown to be negative for HBsAg and positive for anti-HBs at the age of 18 months.
Patients and Methods

- **Group B**: 113 15-year-old volunteer students who had completed 4 doses of plasma-derived HB vaccination during infancy.
- Their serological status against HBV prior to the study was unknown.
Patients and Methods

- All children underwent blood tests for HBsAg, anti-HBs, and anti-HBc.
- A booster dose of 20 µg of a recombinant DNA HB vaccine (Engerix; SmithKline Beecham, Rixensart, Belgium) was given to all subjects in group A and 63 children in group who were HBsAg(-) and whose anti-HBs titer was less than 100mIU/mL.
- Another blood sample was taken 4 weeks after booster vaccination.
- Subjects in group B were offered a second dose of booster if they remained anti-HBs(-) 4 weeks after the first dose of HBV vaccine booster.
HB Markers

- Radioimmunoassays (Ausab, Ausria II, and Corab; Abbott Laboratories, North Chicago, IL) were used to assay anti-HBs, HBsAg, and anti-HBc.

- Anti-HBs concentrations greater than 10 mIU/mL were considered protective. Concentrations between 10 and 100 mIU/mL were considered low titers.

- A carrier was defined as an individual who was HBsAg(+) for more than 6 months.
Table 1. Distribution of Anti-HBs Titers After a Booster Dose of Recombinant Vaccine at the Age of 15 Years and After the Neonatal Vaccination at the Age of 18 Months in 78 Children Born to Mothers Doubly Positive for HBsAg and HBeAg (Group A)

<table>
<thead>
<tr>
<th>Anti-HBs (mIU/mL)</th>
<th>Before Booster* (n = 77)</th>
<th>After Booster at 15 Years of Age</th>
<th>After Neonatal Vaccination at 18 Months of Age</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
</tr>
<tr>
<td>&lt;10</td>
<td>23</td>
<td>29.9</td>
<td>2</td>
</tr>
<tr>
<td>10-100</td>
<td>42</td>
<td>54.5</td>
<td>0</td>
</tr>
<tr>
<td>&gt;100</td>
<td>12</td>
<td>15.6</td>
<td>0</td>
</tr>
</tbody>
</table>

NOTE: This group included one child (1.3%) who was HBsAg-positive and 26 children (33.3%) who were anti-HBc-positive. The HBsAg-positive child was excluded from the booster study. Numbers in parentheses denote case numbers.
*Subjects were grouped by the prebooster anti-HBs titers at the age of 15 years.
Breakthrough HB infection

- One child (Group A) was positive for HBsAg.
- Acquired anti-HBs titer of 21 mIU/mL at the age of 18 months.
- Remained HBsAg(-) at 7 years of age.
- Mixed genotypes B and C in the child, but only genotype B in the mother.
Anti-HBc was detected in 26(33.3%) of the 78 children.

The long-term overall effectiveness of HB neonatal vaccination in maintaining HB disease-free and carrier-free at the age of 15 years were 98.7%(77/78) for all children and 96.2%(25/26) for children with evidence of HBV infection.
Fig. 1. Geometric mean titers of anti-HBs at 18 months of age, before and after a booster dose of recombinant vaccine at 15 years of age in 78 children born to mothers doubly positive for HBsAg and HBeAg (group A). Anti-HBs, hepatitis B surface antigen antibody.
**Table 2. Distribution of Prebooster Anti-HBs Titers in 77 Children Born to HBsAg- and HBeAg-Positive Mothers With Respect to Presence of Anti-HBc at 15 Years of Age (Group A)**

<table>
<thead>
<tr>
<th>Anti-HBs* (mIU/mL)</th>
<th>Anti-HBc–Positive (n = 25)</th>
<th>Anti-HBc–Negative (n = 52)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
</tr>
<tr>
<td>&lt;10</td>
<td>3</td>
<td>12</td>
<td>20</td>
</tr>
<tr>
<td>≥10</td>
<td>22</td>
<td>88</td>
<td>32</td>
</tr>
<tr>
<td>10–100</td>
<td>16</td>
<td>64</td>
<td>26</td>
</tr>
<tr>
<td>&gt;100</td>
<td>6</td>
<td>24</td>
<td>6</td>
</tr>
</tbody>
</table>

**NOTE.** Two children who were anti-HBc-negative and had an initial titer of less than 10 failed to demonstrate a booster response.

*Prebooster anti-HBs titers at 15 years of age were used to categorize children.
Four of these children (3.5%) were positive for HBsAg.

3 of 4 were born to HBeAg(+) mothers and 2 of them received HB immunoglobulin after birth.

The only child-mother pair with available genotyping showed both had genotype B HBV. But the serological status after primary vaccination was unknown.
Table 3. Hepatitis B Serological Markers and Anti-HBs Titers Before and After a Booster Dose of Recombinant Vaccines at the Age of 15 Years in 113 Volunteer Students (group B)

<table>
<thead>
<tr>
<th>Anti-HBs (mIU/mL)</th>
<th>Before Booster (n = 109)</th>
<th>After First Booster (n = 63)</th>
<th>After Second Booster (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
</tr>
<tr>
<td>&lt;10</td>
<td>68</td>
<td>62.4</td>
<td>2</td>
</tr>
<tr>
<td>10-100</td>
<td>27</td>
<td>24.8</td>
<td>0</td>
</tr>
<tr>
<td>&gt;100</td>
<td>14</td>
<td>12.8</td>
<td></td>
</tr>
</tbody>
</table>

NOTE. This group included 4 children (3.5%) who were HBsAg-positive and 5 children (4.4%) who were anti-HBc-positive. The HBsAg-positive children were excluded from the booster study.
Discussion

Four (3.1%) of 128 children with anti-HBs levels of 100mIU/mL or less did not respond to a HB booster vaccine.

The increase of anti-HBs titers after booster at 15 years of age was often blunted, especially for children with low anti-HBs titers after neonatal vaccination.

Children born to mothers who were doubly positive for HBsAg and HBeAg were much more likely to exhibit anti-HBc, a marker of a natural booster effect, than nonselected children representative of the general population.
Discussion

- 41% of children in group A had anti-HBs titers less than 100 mIU/mL. (Suboptimal batches of vaccine?)
- Immune memory was well preserved in most of the children even though waning of anti-HBs was significant.
- For children who had a low response to HB vaccine initially, breakthrough infections might occur 10 to 15 years later.
- It seems reasonable to determine the anti-HBs status of children at 10 to 15 years after receiving plasma-derived HB vaccine and provide a booster to those whose immunity has wanned.
Questions

- The characteristics and durability of antibodies made in response to different vaccines can differ.
- Adolescents born to HBeAg(+) mothers without a protective level of Anti-HBsAb are at high risks of getting HBV infection or becoming HBV carrier?
- Some practice (Safe sex) other than vaccination may be a more cost-effective method for the prevention of HBV infection in adolescents?
Thanks for your attention