Passive Immunization for Infection With
Haemophilus influenzae Type b

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Haemophilus influenzae type b is the leading cause of meningitis in children younger than 5 years of age in the United States. The incidence of infection with H influenzae type b in certain populations, such as Apache and Navajo Indians and Alaskan Eskimos, is 10 to 20 times higher than in the general US population. Another important feature of H influenzae type b infections in these populations is that more than 80% of the cases occur during the first year of life, with 35% to 45% occurring during the first 6 months.

One of the currently licensed vaccines that contains the capsular polysaccharide of the H influenzae type b organism is not reliably immunogenic in infants younger than 18 months of age. A number of new H influenzae type b vaccines prepared by covalently coupling the H influenzae type b capsular polysaccharide with a protein carrier antigen are undergoing clinical evaluation. One of these conjugate vaccines was shown to be efficacious in preventing disease caused by H influenzae type b in Finnish infants when they were immunized at 3, 4, and 6 months of age. Unfortunately, in a recently concluded trial, the same vaccine was not found to be efficacious in preventing such disease in infants younger than 1 year of age among the Alaskan Eskimo population.

We have evaluated an alternative approach for protecting high-risk infants. A human hyperimmune globulin called bacterial polysaccharide immune globulin (BPIG) was prepared from the pooled plasma of adult blood donors immunized with H influenzae type b, pneumococcal, and meningococcal capsular polysaccharide. The pharmacokinetics of antibody to H influenzae type b capsular polysaccharide was compared in older children after BPIG and conventional immune serum globulin were administered intramuscularly at a dose of 0.5 to 0.6 mL/kg. Peak antibody concentrations were approximately 10 times higher after BPIG administration, and concentrations thought to confer protection (>0.15 μg/mL) were maintained for approximately 4 months.

We also have evaluated the efficacy of BPIG in preventing disease caused by H influenzae type b in the Apache Indian population. In addition, we evaluated the effect of administering BPIG simultaneously with a H influenzae type b conjugate vaccine at 2 months of age.

In this brief review we will summarize the findings of these studies and discuss the potential uses of BPIG.

**PHARMACOLOGY OF H INFLUENZAE TYPE b ANTIBODY AFTER BPIG ADMINISTRATION**

Compared with conventional immune globulin prepared from unimmunized donors, BPIG contained approximately 10 times higher concentration of antibody of H influenzae type b capsular polysaccharide. The minimum protective level of passively administered IgG to the H influenzae type b capsule was estimated to be 0.05 to 0.15 μg/mL. This estimate is based on trough antibody levels in patients with agammaglobulinemia receiving conventional immune globulin prophylaxis. In our studies, administration of BPIG at a dose of 0.5 mL/kg resulted in serum H influenzae type b antibody concentrations of >0.15 μg/mL for 4 months in older children and for 3 months in most Apache infants.

**EFFICACY OF BPIG IN PREVENTING INVASIVE H INFLUENZAE TYPE b AND PNEUMOCOCCAL INFECTIONS**

Randomizations

A randomized, double-blind trial was conducted at two Apache Indian reservations from June 1983 to April 1986. Infants born to mothers living in the White Mountain and San Carlos Apache reservations were recruited into the study after written informed consent was obtained.
Protocol

Infants were randomly assigned to receive either BPIG (0.5 mL/kg of body weight) or placebo (0.5 mL of saline) at 2, 6, and 10 months of age. At 2 and 6 months of age, BPIG or placebo was given simultaneously with diphtheria, tetanus, and pertussis immunization. At birth, 2, 4, 6, 10, 15, and 18 months of age, 1 mL of blood was obtained for measurement of serum antibody to the H influenzae type b capsular polysaccharide. If an infant was taken to one of the hospitals or clinics with temperature ≥39°C, blood was obtained for culture and serum was obtained to detect the presence of H influenzae type b antigen. If an infant was thought to have sepsis or meningitis, blood, cerebrospinal fluid, and urine were obtained for bacterial culture and detection of H influenzae type b antigen.

Outcome Measures

Invasive H influenzae type b, pneumococcal, and meningococcal infections, defined as isolation of one of these organisms from a normally sterile body fluid (blood, cerebrospinal fluid, pleural fluid, or joint fluid) were evaluated. Presence of purulent meningitis, defined as >100 polymorphonuclear cells per cubic millimeter of cerebrospinal fluid together with presence of H influenzae type b capsular polysaccharide antigen in the cerebrospinal fluid, was also considered to be invasive disease caused by H influenzae type b.

All infants who received at least one dose of BPIG or placebo were included in the analysis. On the basis of previous pharmacology, only outcomes occurring within 4 months of receipt of BPIG or saline were evaluated for assessment of efficacy.

Results

Of 762 newborn infants recruited into the study, 703 (92%) were randomly assigned to receive at least one dose of BPIG or placebo; 353 were assigned to the BPIG group and 350 to the placebo group. Comparison of various characteristics such as the proportion of infants with low birth weight or the geographic distribution of the population did not show any statistically significant difference between the groups.

The frequency of bacteremic H influenzae type b and pneumococcal infections during the study period is shown in Table 1. As shown in the table, there were no cases of H influenzae type b infections in the BPIG group during the 3-month postimmunization period, whereas seven cases occurred in the placebo group (P = .007). During the fourth month, one case of H influenzae type b infection occurred in the BPIG group. Thus, during the full 4-month period after immunization, one case of invasive disease caused by H influenzae type b occurred in the BPIG group and seven occurred in the placebo group (P = .04). Based on these data, the efficacy of BPIG in preventing disease caused by H influenzae type b during the first 3 months after vaccination was estimated to be 100%, with a 95% one-sided confidence interval of 46.7% to 100%. For the full 4 months, the efficacy was 85.8%, with a 95% confidence interval of −11.4% to 99.7%. During the subsequent follow-up period of 2 years after completion of BPIG and placebo administration, two additional cases of H influenzae type b occurred in the BPIG group and four in the placebo group.

Although fewer cases of invasive pneumococcal disease occurred in the BPIG group compared with the placebo group during the first 3 and 4 months after immunization, these differences were not statistically significant.

We also have estimated a pooled efficacy rate for BPIG in the prevention of H influenzae type b bacteremias by comparing the incidence of H influenzae type b bacteremias during infancy in all BPIG recipients with that in all untreated individuals. The placebo recipients and all nonparticipating infants were pooled because their H influenzae type b bacteremia incidence was similar. The efficacy was approximately 88%, with a 95% confidence interval of 60% to 95%.

Since the completion of this trial, we have provided BPIG to all infants in this population during the first year of life. Because this population continues to experience a high attack rate of pneumococcal disease during the second year of life, we are conducting further studies to evaluate the efficacy of BPIG in preventing pneumococcal infections during the second year.

Efficacy of BPIG in Preventing Other Infections

During the first phase of the study, significant reductions were noted in the numbers of children with recurrent pneumonia (more than three episodes) and children hospitalized with fever ≥39°C in the BPIG group. However, the frequency of all roentgenographically documented pneumonia, clinically diagnosed otitis media, or gastroenteritis did not differ significantly between BPIG and placebo groups.

Studies of experimental otitis media in chinchillas suggest that passive immunization with BPIG is effective in the prevention of pneumococcal otitis media. Therefore, a pilot study of BPIG in the prevention of recurrent otitis media was performed in high-risk infants in Cleveland, Ohio. Infants with 1 to 3 prior episodes of otitis media were given
TABLE 1. *Haemophilus influenzae* Type b (Hib) and Pneumococcal Bacteremia in Infants Given Bacterial Polysaccharide Immune Globulin (BPIG) or Placebo

<table>
<thead>
<tr>
<th></th>
<th>BPIG Group</th>
<th>Placebo Group</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients at risk</td>
<td>353</td>
<td>350</td>
<td></td>
</tr>
<tr>
<td>No. of doses</td>
<td>858</td>
<td>838</td>
<td></td>
</tr>
<tr>
<td>Cases of invasive disease caused by Hib</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before treatment period</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-90 days after immunization</td>
<td>0</td>
<td>1</td>
<td>.007</td>
</tr>
<tr>
<td>91-120 days after immunization</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>After treatment period†</td>
<td>2</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Cases of invasive pneumococcal infections</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before treatment period</td>
<td>1</td>
<td>0</td>
<td>.06</td>
</tr>
<tr>
<td>1-90 days after immunization</td>
<td>0</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>91-120 days after immunization</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>After treatment period†</td>
<td>6</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Combined no. of cases of invasive Hib and pneumococcal infections</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before treatment period</td>
<td>1</td>
<td>1</td>
<td>.007</td>
</tr>
<tr>
<td>1-90 days after immunization</td>
<td>0</td>
<td>11</td>
<td>.001</td>
</tr>
<tr>
<td>91-120 days after immunization</td>
<td>3</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>After treatment period†</td>
<td>8</td>
<td>10</td>
<td></td>
</tr>
</tbody>
</table>

* By two-sided Fisher's exact test. P value is given only if P < .1.
† From 121 days to 2 years after the third dose.

two doses of BPIG (0.5 mL/kg) 1 month apart and observed for a total of 4 months. The bacteriology of otitis media was examined by tympanocentesis. A significant reduction in pneumococcal otitis media was observed in BPIG-treated infants (7 episodes in 37 BPIG patients as compared with 18 episodes in 42 placebo patients). However, the frequency of otitis media associated with *H influenzae* (nontypable), *Branhamella catarrhalis*, or negative cultures was not decreased. As a consequence, the frequency of all episodes of otitis media was not significantly decreased by BPIG prophylaxis.

**BPIG AND CONJUGATE VACCINES**

We randomly assigned 2-month-old Navajo infants to one of three groups. Group 1 (control group) was not immunized against *H influenzae* type b; group 2 received a new *H influenzae* type b conjugate vaccine termed HbOC (Praxis Biologics, Rochester, NY) at 2, 4, and 6 months of age; and group 3 received HbOC at the same ages as group 2 and also received one dose of BPIG at 2 months of age. (The HbOC vaccine is composed of *H influenzae* type b capsular polysaccharide covalently linked to nontoxic diphtheria toxin cross-reactive material.) Blood samples were drawn from all three groups just before each immunization and at 7 and 12 months of age.19

The mean *H influenzae* type b capsular polysaccharide antibody levels and the proportion of infants with *H influenzae* type b capsular polysaccharide levels ≥0.15 μg/mL and ≥1 μg/mL are shown in the Figure and Table 2. Infants who received BPIG simultaneously with their first dose of HbOC at 2 months (group 3) had significantly higher antibody concentrations when compared with the other two groups at 4 months (P < .001). The antibody response to the second and third injections of HbOC was similar in the group that re-
TABLE 2. Antibody Response to Haemophilus influenzae Type b (Hib) Capsular Polysaccharide (CP) of 2-, 4-, and 6-month-old Navajo Infants Immunized With HbOC Vaccine Alone or Combined With Bacterial Polysaccharide Immune Globulin (BPIG)

<table>
<thead>
<tr>
<th>Age, mo</th>
<th>Geometric Mean Hib CP Antibody, μg/mL</th>
<th>% With Antibody ≥0.15 μg/mL</th>
<th>% With Antibody ≥1 μg/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unimmunized</td>
<td>HbOC Alone</td>
<td>HbOC + BPIG</td>
</tr>
<tr>
<td></td>
<td>Control (n=25)</td>
<td>(n=26)</td>
<td>(n=24)</td>
</tr>
<tr>
<td>2</td>
<td>0.23</td>
<td>0.19</td>
<td>0.16</td>
</tr>
<tr>
<td>4</td>
<td>0.11</td>
<td>0.12</td>
<td>0.76*</td>
</tr>
<tr>
<td>6</td>
<td>0.11</td>
<td>1.28‡</td>
<td>1.53‡</td>
</tr>
<tr>
<td>7</td>
<td>0.11</td>
<td>10.5‡</td>
<td>8.82‡</td>
</tr>
<tr>
<td>12</td>
<td>0.075</td>
<td>1.43‡</td>
<td>2.06‡</td>
</tr>
</tbody>
</table>

* Differs from HbOC-alone group at P < .001.
† Differs from HbOC-alone group at P < .05.
‡ Differs from control group at P < .001.
§ Differs from control group at P < .05.

received HbOC alone compared with the group that received HbOC and BPIG. Infants who had received the passive-active immunization regimen had decreases (81% median decrease over 5 months) similar to those of infants who received active immunization alone.

CONCLUSION

Passive immunization with BPIG at a dose of 0.5 mL/kg every 4 months reduced bacteremic H influenzae type b infections by approximately 88% in Apache infants. Protection was most reliable during the first 3 months after immunization; breakthrough infections were occasionally observed after 3 months. BPIG did not interfere detectably with the active antibody response to simultaneously administered diphtheria, tetanus, and pertussis vaccine or HbOC conjugate vaccine. The acquisition of antibodies to H influenzae type b polysaccharide by natural exposure was not delayed by BPIG administration (G. S., M. S., and R. P., unpublished data, 1987). Similarly, the maturation of the capacity to respond to purified H influenzae type b polysaccharide was not affected by passive immunoprophylaxis.

Although it is more expensive than active immunization, BPIG prophylaxis may be cost-effective for the prevention of severe H influenzae type b infections in high-risk populations such as American Indian and Eskimo infants. As more immunogenic conjugate vaccines become available, regimens combining passive and active immunization may provide uninterrupted protection at lower cost.

Another potential use for BPIG would be as prophylaxis for the exposed household contacts of patients with primary H influenzae type b infection. Currently, rifampin prophylaxis is recommended for all household contacts in this situation. In contrast with rifampin prophylaxis, BPIG prophylaxis could be administered only to the young children who are themselves at risk.

If BPIG is shown to be efficacious in preventing pneumococcal infections, indications for its use may be broadened to include individuals at high risk for these infections, such as children with sickle cell disease and asplenia, or those receiving chemotherapy for cancer.

REFERENCES


Passive Immunization for Infection With *Haemophilus influenzae* Type b
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