Efficacy of Heptavalent Pneumococcal Conjugate Vaccine in Children With Cochlear Implant

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Objective: The aim is to analyze the efficacy of heptavalent conjugate vaccine against *Streptococcus pneumoniae* (VPn7) in children with cochlear implant, in relation with the eradication of nasopharyngeal carriers and the prevention of complications. Analysis of the antimicrobial resistance and sensitivity of the different pneumococci strains isolated in cochlear implant nasopharyngeal carriers and healthy non-vaccinated children.
Method: Pneumococcal nasopharyngeal carriers were analyzed in this prospective study including 2 groups of children aged between 2 and 5 years, from 2005 to 2006. The first group included 55 cochlear implant recipients and all of them were vaccinated with VPn7. The second group included 60 non-vaccinated healthy children. Nasopharyngeal swabs for culture were obtained from each child in order to detect the pneumococcus, its serotypes, and the sensitivity to antibiotics.
Results: In the control group of non-vaccinated children, 25% of them were found to be pharyngeal pneumococcus carriers, whereas this figure fell to 11% in the vaccinated group. The non-vaccine serotypes (83.3%) isolated in vaccinated children showed high or moderate sensitivity to penicillin. There were no complications due to *S pneumoniae* infections in any of the patients with cochlear implant who were vaccinated.
Conclusions: VPn7 contributes to a decrease in pharyngeal colonization by pneumococci in general and, in particular, by the pneumococcal serotypes included in the vaccine, although there is a replacement phenomenon involving non-vaccine serotypes.

Key words: *Streptococcus pneumoniae*. Nasopharyngeal carrier status. Pneumococcus vaccine.

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Efecto de la vacuna heptavalente contra *Streptococcus pneumoniae* en niños con implante coclear

Objetivo: Analizar la eficacia de la vacunación conjugada heptavalente contra *Streptococcus pneumoniae* (VPn7) en niños con implante coclear en la eliminación de portadores nasofaríngeos y la prevención de complicaciones. Análisis de resistencia y sensibilidad a los antimicrobianos de las cepas de neumococos aisladas tanto en portadores nasofaríngeos con implante vacunados como en niños sanos no vacunados.
Método: Se estudia el estado de portador nasofaríngeo de neumococo mediante un análisis prospectivo en dos grupos de niños de 1 a 5 años de edad, durante los años 2005 y 2006. Un grupo incluye a 55 niños con implante coclear y vacunados con VPn7, y un segundo grupo está formado por 60 niños sanos sin vacunación. De cada paciente se recogieron muestras nasofaríngeas para la detección de neumococo, sus serotipos y su sensibilidad a antibióticos.
Resultados: El análisis del grupo control no vacunado presenta un tasa de portadores de neumococo en faringe del 25%, mientras que esta cifra disminuye al 11% en el grupo de niños vacunados. Los serotipos no vacunales (83,3%) aislados en pacientes vacunados, mostraban sensiblilidad alta o moderada a penicilina. No se han producido complicaciones a causa de infecciones por *S. pneumoniae* en ninguno de los pacientes implantados y vacunados.
Conclusiones: La VPn7 contribuye a la disminución de la colonización faríngea por neumococo en general y, en particular, por los serotipos de neumococo incluidos en la vacuna, aunque se produce un fenómeno de remplazo por serotipos no vacunales.

Palabras clave: *Streptococcus pneumoniae*. Estado de portador nasofaríngeo. Vacuna neumocócica.

INTRODUCTION

An epidemiological study performed by the Spanish Society of Otorhinolaryngology and the Ministry of Health and Consumer Affairs showed an increase in the incidence

of meningitis during the years 2000-2001, related to the use of cochlear implant systems that included external electrode positioners.[1] At the beginning of 2004, the indication of a systematic vaccine against *Streptococcus pneumoniae* was approved in the cochlear implant population, as they are considered at risk.[2,3]

The general recommendations outlined by different organizations for the prevention of bacterial meningitis in carrier patients or candidates for cochlear implants are the following: diagnosis and treatment of otitis, before and after the placement of an implant; antibiotic prophylaxis in surgery, and anti-pneumococcal vaccine, vaccine against *Haemophilus influenzae* type b (Hib), and anti-meningococcal vaccine.

The conjugate vaccines against Hib and meningococcus C are already part of the series of systematic immunizations in Spain. The patients wearing cochlear implants are, thus, candidates for anti-pneumococcal immunization.

The VPn7 vaccine is indicated for the active immunization of infants older than 2 months and children younger than 5 years against invasive disease (including bacteraemia, sepsis, meningitis, and bacteraemic pneumonia) caused by *S pneumoniae.*

On the other hand, its efficacy against otitis media is estimated at 65% of those produced by serotypes included in the vaccine; the efficacy in the prevention of pneumococcal otitis in general is 34%, and does not surpass 6% of all cases of otitis media.[4,5]

The pharynx is the location where strains of *S pneumoniae* can be selected and later be disseminated. Resistant pneumococcus presents a greater dissemination potential in humans than sensitive strains.[6,7]

It is of fundamental importance to identify the distribution of the most prevalent serotypes in carriers in a specific country, since one of the fundamentals for the preparation of the vaccines currently available is, precisely, the induction of a type-specific immune reaction aimed at capsular polysaccharides of the strains isolated in carriers and in pneumococcal infections.

PATIENTS AND METHOD

As the maximum incidence of pneumococcal infection in the upper respiratory tract is produced at ages between 0 and 5 years, 115 children in this age group have been included and distributed into 2 groups:

– Control group (n=60). An analysis has been made of the pneumococcal serotypes colonizing the pharynx of unvaccinated healthy children, without prior otorhinolaryngological illness during the previous 6 months and not taking antibiotics for any other reason

– Group of vaccinated children (Vpn7) with cochlear implant (n=55). An analysis has been made of the pneumococcal serotypes colonizing the pharynx of these children. A check was made as to whether any of them suffered from otitis media or any other type of pneumococcal infection during the study period following the implant; this follow-up protocol includes reviews at 3, 6, and 12 months, and once every 6 months thereafter

Vaccination was administered prior to the cochlear implant, and was applied in accordance with the guidelines corresponding to their ages.

The pneumococcal serogroups included in the current vaccine (Vpn7) are 18C, 4, 6B, 9V, 18C, 14, 19F, and 23F.

Vaccination Program

Vaccination regime according to age at the start of vaccination:

– Children from 2 to 6 months: 3 doses of conjugate vaccine 2 months apart and a booster dose at 12-15 months

– Children from 7 to 11 months: 2 doses of conjugate vaccine 2 months apart and a booster dose at 12-15 months

– Children from 12 to 23 months: 2 doses of conjugate vaccine 2 months apart

– Children from 2 to 5 years: 1 dose of conjugate vaccine.

The vaccination regime should be completed with 1 dose of 23-valent polysaccharide vaccine (sequential vaccination, at least 8 weeks after the last dose of conjugate vaccine)

The conjugate vaccine is heptavalent, and the one available in Spain is Prevenar (Wyeth Lederle Vaccines SA).

All the samples for analysis of the carriers are obtained through nasopharyngeal smear and are processed for bacteriological study through conventional culture and identification techniques. The isolation of *S pneumoniae* was done on a blood agar plate, incubated for 24-48 hours in an atmosphere of CO_2 (5%-10%) at a temperature of 37ºC. The identification of the *S pneumoniae* isolates was performed by testing their sensitivity to a 5 mg optochin disc, latex agglutination (bioMérieux Slidex pneumo-kit, France), and solubility in bile. Sensitivity to antibiotics was determined through their minimum inhibitory concentrations (MIC) by broth microdilution (WIDER, Soria Melguizo). The reading and interpretation of the results followed the criteria of the National Committee for Clinical Laboratory Standards (NCCLS). The strains of *S pneumoniae* were subsequently sent to the Department of Bacteriology of the National Microbiology Centre at the Carlos III Health Institute in Madrid, to determine the serotypes of the strains identified.

Data analysis: the descriptive analysis was done in terms of percentages.

RESULTS

Control Group (n=60): Unvaccinated Healthy Children

Of the 60 children studied, 25% were carriers of pneumococcus in the pharynx (n=15). The mean age of presentation was 3.2 years. The mode was 3 years. The distribution by sex was 53.3% female and 46.6% male.

Table 1. Serotypes Isolated in Healthy Unvaccinated Children, With Their Respective Minimum Inhibitory Concentration Values for the Antibiotics Tested[a]

Serotypes	*Penicillin*	*Erythromycin*	*Cefotaxime*	*Levofloxacin*
19A	S-0.015	R-128	S-0.015	S-1
19A	R-2	R-128	R-2	S-1
19A	S-0.03	R-128	S-0.015	S-1
19F	S-0.06	R-128	S-0.03	S-1
9V	R-2	S-0.12	I-1	S-1
11	S-0.015	S-0.12	S-0.015	S-1
14	S-0.015	R-64	S-0.015	S-1
18C	S-0.015	S-0.12	S-0.015	S-1
24	R-2	R-128	S-0.250	S-1
24	I-0.5	R-128	S-0.120	S-1
24	I-0.5	R-128	S-0.120	S-1
24	I-0.5	R-128	S-0.120	S-1
6B	I-1	R-128	S-0.500	S-1
23F	S-0.015	S-0.12	S-0.015	S-1
3	S-0.015	S-0.12	S-0.015	S-1

[a]I indicates intermediate; R, resistant; S, sensitive.

Table 2. Serotypes Isolated in Vaccinated Children and Age at Which Vaccination Was Started

Serotype	*Age, Years*	*Age at Start of Vaccination*
42	5	1
19A	1.6	<1
19F	4	1
15A	5	2
7F	2	1
3	5	1

Table 3. Serotypes Isolated in Vaccinated Children, With Their Respective Minimum Inhibitory Concentration Values for the Antibiotics Tested[a]

Serotypes	*Penicillin*	*Erythromycin*	*Cefotaxime*	*Levofloxacin*
42	I-0.12	32	0.06	S-1
19A	I-0.5	128	0.25	S-1
19F	R-2	128	1	S-1
15A	S-0.025	128	0.12	S-1
3	S-0.015	0.12	0.015	S-1
7F	S-0.015	0.12	0.015	S-1

[a]I indicates intermediate; R, resistant; S, sensitive.

Only 1 serotype was isolated in each patient, so the number of serotypes obtained corresponds to the number of carrier patients, 25% (Table 1).

Of the 15 carrier patients, 7 had serotypes included in the conjugate vaccine (19F, 9V, 14, 18C, 6B, and 23F), ie, 46.6% of the serotypes found.

Serotypes 6B and 24 presented intermediate sensitivity to penicillin (MIC ≥0.12-1 µg/mL), while a strain of serotypes 19A, 9V, and 24 presented penicillin-resistant MICs (≥2 µg/mL). The other isolates (53%) were sensitive. Cefotaxime retains good activity against pneumococcus.

Resistance to macrolides deserves special mention, as this was observed in 66.6% of cases. All strains are sensitive to levofloxacin.

Group of Vaccinated Children With Cochlear Implants (n=55)

Of the 55 children who had received the vaccine (Vpn7), 10.9% were pharyngeal carriers of pneumococcus. Mean age of presentation was 3.7 years and the mode was 5 years. The distribution by gender was 50% female and 50% male. Anti-pneumococcal vaccination in 80% (n=44) of cases was prescribed at 12 months of age at the out-patient clinic for hearing loss, once the need for a cochlear implant was already indicated in those children. Other patients (14.5%; n=8) were vaccinated between 14 and 23 months of age, depending on the time when they arrived at the hearing loss out-patient clinic for indication of an implant. Only 1 child was vaccinated during the first year of life. Lastly, 2 other children included in the study (3.6%) were vaccinated after 24 months of age (Table 2).

Of the 6 carrier patients, 5 had serotypes not included in the conjugate vaccine. Only in 1 child was a strain with vaccine serotype 19F isolated, which was also the serotype most resistant to antibiotics isolated in this group; its MIC to penicillin was >2 µg/mL and it also showed an intermediate sensitivity to cefotaxime. Serotypes 42 and 19A presented intermediate sensitivity to penicillin, and the rest of the strains were sensitive.

Only 33.3% of the strains were sensitive to macrolides and 100% to levofloxacin (Table 3).

During the follow-up period with implanted children, there were no complications owing to *S pneumoniae*.

DISCUSSION

Implants, as they are foreign bodies, may raise the risk of colonization and dissemination of bacterial infections. Young children are particularly sensitive patients because they do not identify pain in the ears and tend to complain non-specifically. Pneumococcal meningitis, in addition to being a result of bacteraemia, can be produced as a consequence of a direct extension from the paranasal sinuses or the middle ear. An invasive pneumococcal disease is defined as any infection in which *S pneumoniae* is isolated in the blood or other normally sterile zone. In Spain, the incidence of morbidity and mortality from pneumococcus is lower than that published in neighbouring countries, and even though the vigilance systems used are different, it seems that the incidence of invasive disease is underestimated in our country.[8]

In infants less than 2 years of age or included in risk groups, as is the case with recipients of cochlear implants, the Vaccination Assessment Committee of the Spanish Paediatric Association recommends vaccination with conjugate vaccines against pneumococcus, as they are safe and effective in the prevention of invasive disease. Conjugate vaccines allow the production of the largest number of antibodies and the development of immunological memory. In addition, this type of response can be observed from the first months of life. All 3 of these characteristics differentiate it from a single polysaccharide vaccine.

The prevention of otitis media is also important as, although it is not a serious infection at first, it is a great limitation on the lives of these children.[9-11] In the study presented, no complication from *S pneumoniae* was observed in the children with implants.

The serogroups included in the current heptavalent vaccine (18C, 4, 6B, 9V, 14, 19F, and 23F) would cover 83% of the strains causing meningitis, 86% of those of pneumonia, and 65% of the producers of otitis, but their clinical efficacy is very variable. In the absence of sufficient data in Spain on the epidemiology of pneumococcal disease, we have taken current data for the United States as our benchmark, as there is wide vaccine coverage and good epidemiological monitoring.[12,13] In another study, also performed in the United States,[14] the rates of invasive disease due to resistant strains diminished in children and adults. The reduction in the resistance of invasive pneumococcal strains in children has also occurred in Spain.[15,16] The data that this study provides refer to pharyngeal colonizing strains and none of them produced an infection; the unvaccinated control group presented a 25% rate of pharyngeal pneumococcus carriers whereas this figure went down to 11% in the group of vaccinated children; the study on carriers could explain why, unlike the bibliography consulted, we did not observe meaningful variations with respect to sensitivity to penicillin between those vaccinated and those unvaccinated. There were also no different sensitivity behaviours between the 2 groups vis-à-vis macrolides or quinolones.

What is clearly observed in vaccinated children is that a replacement effect has occurred in the pneumococcal serotypes colonizing the pharynx; in only 1 child was a strain isolated with the vaccine serotype 19F, which was also the serotype most resistant to antibiotics isolated in this group; the rest of the serotypes isolated were not included in the Vpn7 vaccine.

Since the availability of the new heptavalent conjugate vaccine, there has been a considerable increase in the interest in improving both the epidemiological awareness of invasive disease caused by pneumococcus as well as the coverage of the vaccine serotypes causing illness in our setting. However, there are still various aspects that must be clarified. In Spain, the rate of children carrying pharyngeal pneumococcus was estimated at 36% in 1999,[17] a figure somewhat greater than those found in our community in the years 2005 and 2006. One question under discussion is the effect of the vaccine on pneumococcus carriers and the possibility of selecting pneumococcus strains not included in the vaccine. There is no single answer to these questions, hence the importance of the performance of epidemiological vigilance studies into the current colonizing and invading serotypes in order to determine whether the ones not covered by the vaccine become more prevalent after its introduction.

Vaccination against pneumococcus in children with cochlear implants avoids the complications produced by this bacterium; in the study presented there is no case of invasive sickness or of otitis media. The Vpn7 vaccine contributes to the reduction of pharyngeal colonization by pneumococcus in general, and, in particular, by the serotypes of pneumococcus included in the vaccine, even though there is a replacement phenomenon by non-vaccine serotypes. In our setting, sensitivity to penicillin (50%), erythromycin (33%), and levofloxacin (100%) is similar in vaccine and non-vaccine serotypes.

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