Long-term effects of dexamethasone on hearing ability in children with pneumococcal meningitis

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Controlled trials concerning adjuvant dexamethasone therapy in bacterial meningitis do not point unequivocally to a beneficial effect on hearing ability. We investigated the remote adverse outcomes of pneumococcal meningitis and, if any, beneficial effects of adjuvant dexamethasone therapy on hearing ability. Fifty-five subjects who experienced pneumococcal meningitis between 1987-97 were divided into two groups as 25 subjects who did not receive dexamethasone (Group 1) and the remaining 30 subjects who did (Group 2). All subjects underwent pure tone thresholds estimation. There were a total of 11 subjects (20%) with sensorineural hearing impairment (SNHI): 6 in the first group (24%) and 5 in the second group (16%). Although there was no statistically significant difference in the SNHI ratio between the groups, all the subjects who used adjuvant dexamethasone therapy suffered only minimal-borderline SNHI, whereas 2 patients in Group 1 had moderate-serious SNHI. Even though adjuvant dexamethasone therapy had no statistically significant impact on hearing ability after long-term follow-up, its use may be a good choice in terms of preventing serious SNHI.

Key words: dexamethasone, pneumococcal meningitis, hearing impairment.

Bacterial meningitis is a severe childhood illness. The overall mortality declined significantly with the use of potent wide-spectrum antibiotics and advances in care of the critically ill patient. On the other hand, a substantial ratio of survivors suffer mild or serious handicaps. Sensorineural hearing impairment (SNHI) is a known sequela of meningitis with varying incidence rates of 3.5% to 37.2% according to reports[1,2]. In a critical review, Fortnum[3] stated the overall incidence rate following bacterial meningitis as 9.6%.

The results of many controlled trials concerning adjuvant dexamethasone therapy in bacterial meningitis do not point unequivocally to a beneficial effect in children. A recent meta-analysis showed a beneficial effect in children with Haemophilus influenzae type b meningitis and suggested a protective effect in those with pneumococcal meningitis if dexamethasone was given before or with parenteral antibiotics[4].

The aim of this study was to investigate the long-term beneficial effects of adjuvant dexamethasone therapy on hearing ability in pneumococcal meningitis (PM) subjects.

Material and Methods

Postmeningitic Cohort

The study was carried out between June 2003 and March 2004. Archives of a tertiary-care teaching hospital, Hacettepe University Medical Faculty İhsan Doğramacı Children's Hospital, were screened for data on eligible patients. The inclusion criteria comprised the

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files catalogued under the topic "pneumococcal meningitis" between the years 1987-1997. The exclusion criteria were "complex-onset" of meningitis (defined as meningitis secondary to cranial trauma, central nervous system surgery, immunodeficiency states, or relapsing meningitis) and diseases developed before and after meningitis (e.g., leukemia) that could have caused extra sensorial damage and cognitive problems. This last criterion was applied as these patients were also included as part of a study on long-term effects of dexamethasone on behavioral problems and academic success after bacterial meningitis.

The inclusion criteria were met by 141 files. The patients were contacted after obtaining their contact information from within their files. For those with missing contact data, we conducted an internet search of unknown phone numbers and addresses, searched via parental data, and utilized a national telecommunications company (www.ttrehber.gov.tr). Unfortunately, 68 subjects could not be evaluated due to: no available telephone number at the time of admission (n=39), relocated to another city/country (n=14), no permission from parent (n=4), death due to meningitis complications (n=6), death for other reasons (n=2), unavailability due to military service (n=1), and university education/working in another city (n=2). Moreover, an additional 18 children were excluded because of meningitis with "complex-onset" (n=15) and diseases after meningitis that could have caused extra sensorial damage and cognitive problems (n=3).

Thus, the remaining 55 patients were organized into two groups as 1) 25 subjects who did not receive adjuvant dexamethasone therapy (Group 1), and 2) the remaining 30 subjects who did receive dexamethasone (Group 2). All the subjects in the second group had no previous history of antibiotics, and received 0.6 mg/kg/day intravenous (iv) dexamethasone divided into four daily doses for four days. Subsequently, medical records of the children were studied to obtain admission and follow-up data.

Evaluation of Hearing Levels

All audiological tests were performed at Hacettepe Medical Faculty, Department of Ear, Nose and Throat, Division of Hearing and Speech by the same specialist to avoid variation in technique; the specialist had no information on group randomization. Interacoustics AC-40 audiometry device and TDH-49 earphones were used for audiological testing. For testing higher frequencies, KOSS R80 device and Interacoustic AS-10 HF device along with KOSS HV PRO earphones were used. In addition, B71 bone vibrator was used for bone-conduction threshold measurements.

All subjects underwent air-conduction and bone-conduction pure tone threshold estimation at 125-16000 Hertz (Hz) frequencies, and threshold levels were noted in decibel (dB). In addition, each subject was evaluated by an audiologist according to hearing loss classification by Clark[5] (Table I).

Table I. Classification of Degree of Hearing Impairment

Degree of hearing loss	
-10 to 15 dB	Normal (0)
16-25 dB	Borderline-slight hearing loss (1)
26-40 dB	Mild hearing loss (2)
41-55 dB	Moderate hearing loss (3)
56-70 dB	Moderate-severe hearing loss (4)
71-90 dB	Severe hearing loss (5)
>90 dB	Profound hearing loss (6)

dB: Decibel.

We observed two subjects with middle ear infection and evaluated their hearing ability after appropriate therapy. In order to differentiate conductive type hearing loss, each patient underwent testing of acoustic reflex and measurement of middle ear pressure by the help of impedance meter, Zodiac 901.

Statistical Analysis

The data obtained by retrospective investigation of patient files and prospective evaluation of subjects were analyzed by SPSS for Windows Release 13, SPSS Inc, USA and EPI Info 6.0, CDC-Atlanta, USA, with the help of the Department of Biostatistics in İnönü University Medical Faculty.

The difference between the two groups was studied by independent samples t-test and χ^2. Statistical significance was considered when P values <0.05 for all tests.

Results

There were no differences between groups concerning the mean age, mean age at diagnosis and elapsed time after meningitis (Table II). The youngest subject at the time of diagnosis was 5 weeks and the oldest was approximately 15 years old. At the present evaluation, the age range was between 5.2 - 21 years old. The evaluation of cerebrospinal fluid (CSF) biochemistry, hemogram and infection parameters were almost similar between the groups, except for a statistically significant lower CSF neutrophil count in the first group (Table II). The high rate of previous antibiotic therapy at admission (60%) might be a reason for decreased CSF neutrophil value in this group. The microbiological results are presented in Table III. Diagnosis of pneumococcal meningitis was established using latex agglutination (62%), CSF culture (38%), Gram staining (36%) and blood culture (4%). The low rate of CSF culture-positive results (30%) in the first group might be due in part to the high rate of previous antibiotic therapy (60%), but this is not valid for the 2nd group's ratio (45%). The lower than expected ratio of CSF culture-positive results in this study in fact depends on many occasions on missing/unfilled data in the related pages of the binders.

All subjects underwent air-conduction and bone-conduction pure tone threshold estimations at the aforementioned frequencies, and threshold

Table II. Clinical and Laboratory Characteristics of the Study Groups at the Time of Diagnosis

Characteristics	Group 1 (Dexamethasone untreated)	Group 2 (Dexamethasone treated)
n	25	30
Age at present evaluation (yrs)	12.99±4.48	13.18±4.07
Age at diagnosis (yrs)	5.88±3.61	5.77±4.29
Elapsed time after meningitis (yrs)	7.11±2.41	7.40±2.42
CSF protein (mg/dl)**	218±55	258±78
CSF glucose (mg/dl)	51±27	45±19
CSF/serum glucose (%)	42±10	39±12
CSF total cell count	946±700	1349±944
CSF neutrophil count	412±355*	962±772
CSF lymphocyte count	73±72	66±65
Hb (g/dl)	12.4±1.7	12.0±1.5
WBC (x1000/ml)	12.1±6.1	11.8±6.5
Platelet (x1000/ml)	309±139	291±108
ESR (mm/hr)	57±31	58±24
CRP (mg/dl) (N<0.6)	4.0±4.5	8.2±9.1

* $p<0.05$.
** All laboratory values belong to the evaluation at the time of diagnosis.
CSF : Cerebrospinal fluid. Hb: Hemoglobin. WBC: White blood cell. ESR: Erythrocyte sedimentation rate. CRP: C-reactive protein.

Table III. Microbiological Evaluation of Study Groups

Characteristic	Group 1 (Dexamethasone untreated)	Group 2 (Dexamethasone treated)
n	25	30
CSF culture	8 *S pneumoniae*	13 *S pneumoniae*
Blood culture	1 *S pneumoniae*	1 *S pneumoniae*
Gram stain	5 *S pneumoniae*	15 *S pneumoniae*
Latex agglutination	19 *S pneumoniae*	15 *S pneumoniae*

CSF: Cerebrospinal fluid.

levels were noted in dB. One of the subjects in the second group had developed severe motor-mental retardation after PM. He was accepted as "probably having normal hearing function" since he was actively responding upon receiving audiological stimulus, but he was not included in the evaluation of hearing thresholds. The bilateral air-conduction thresholds are summarized in Table IV. Although the hearing thresholds of the second group were better at all frequencies, the only statistically significant values were at higher frequencies: 10,000 dB for both ears and at 12000 dB for the left ear.

There were a total of 11 patients (20%) with varying degrees of SNHI in the whole population (Table V). There was no statistical difference in the SNHI ratio between the two groups. However, the PM subjects with adjuvant dexamethasone therapy suffered only minimal-borderline SNHI when compared to two patients with moderate-severe SNHI in the first group. Of these 11 subjects, only four had previous audiometric results in the relevant binders. One subject had serious deterioration in hearing, one child had improvement but still experienced unilateral minimal SNHI, and the remaining two subjects had similar minimal SNHI.

Twenty-nine (52.7%) parents recalled having their children's hearing evaluated after meningitis, but only 22 (40%) test results were available in the binders. All 22 of these patients had undergone similar audiological tests at Hacettepe Medical Faculty, Department of Ear, Nose and Throat, Division of Hearing and Speech. In the evaluation of hearing six weeks after meningitis, five patients (22%) had SNHI. All five patients had experienced minimal SNHI. Two of these previously minimally impaired five patients had improved audiological testing and at present have no abnormality. One child exceptionally experienced marked deterioration in hearing ability, and the remaining two patients had similar unilateral minimal SNHI at the present evaluation.

As a result, we were able to compare all the available past audiological findings of 22 patients with the present data. We showed that the majority of the subjects, 19 cases (86%), demonstrated no difference in hearing

Table IV. Bilateral Air-Conduction Thresholds at Related Frequencies

Frequencies	Ear	PM without dexamethasone (n=25)	PM with dexamethasone (n=29)*
250	Right	21.2±21.2	15.8±7.4
	Left	14.0±7.5	11.5±5.1
500	Right	16.6±21.4	11.2±6.2
	Left	10.2±5.2	8.4±4.2
1000	Right	11.8±22.9	6.2±6.3
	Left	7.0±7.0	4.8±3.8
2000	Right	11.2±23.5	5.1±6.1
	Left	4.8±6.3	3.7±4.5
4000	Right	11.4±23.4	5.5±5.2
	Left	6.4±8.9	6.3±6.5
8000	Right	13.4±23.5	5.6±7.0
	Left	9.4±7.4	6.9±6.3
10000	Right**	14.0±14.8	7.4±9.6
	Left**	12.4±12.2	5.5±8.3
12000	Right	13.2±25.2	9.3±16.8
	Left**	11.2±12.8	4.1±9.2
14000	Right	15.8±27.4	11.2±14.1
	Left	10.4±15.0	5.5±9.8
16000	Right	19.6±29.9	16.2±17.6
	Left	16.0±21.1	11.3±13.6

* Results for one subject with severe motor-mental retardation not included.
** $p<0.05$.

Table V. Summary of Patients with SNHI after Bacterial Meningitis

Group 1 (Dexamethasone untreated)	Right	Left
I	4S	2S
II	N	1S
III	N	1S
IV	N	5S
V	1S	1S
VI	1S	N
Group Summary	6 subjects (24%) have SNHI, of which 2 are unilaterally severe	
Group 2 (Dexamethasone treated)	**Right**	**Left**
I	1S	1S
II	1S	1S
III	1S	1S
IV	N	1S
V	1S	N
Group Summary	5 subjects (16%) have minimal-borderline SNHI	
General Summary	11 subjects (20%) with SNHI (2 subjects with severe type)	

Gradings between 1-5 explained in Table I.
S: Sensorineural type hearing impairment. N: Normal hearing thresholds.

ability at present. As mentioned above, two of the subjects (9%) had minimal improvement in hearing, and one subject in the first group had markedly deteriorated hearing ability (Table VI).

Discussion

Bacterial meningitis is the leading etiological cause of acquired SNHI in childhood[6]. Since profound or total SNHI disrupts the development of communication skills, particularly in young children who have not fully developed speech and language skills, pediatricians must be sufficiently alert to not overlook this sequela. In addition, partial and/or unilateral SNHI needs to be diagnosed with minimal delay as these subjects may suffer auditory and linguistic disabilities.

As previous studies were limited to evaluations performed within one or two years of follow-up, the long-term sequelae may have been underestimated. We wanted to investigate remote adverse outcomes of bacterial meningitis by long-term follow-up. The mean time for elapsed period after PM was almost 7.2 years for the study group, with a range of 5 to 14.5 years (Table II). The total number of subjects with SNHI was 11 (20%) after PM in our cohort, which is compatible with the literature[7,8]. Although the SNHI rate was not significantly high in the dexamethasone-untreated group (24%) when compared to treated group (16%) ($p>0.05$), all five subjects who used dexamethasone had slight SNHI that could only be detected by audiological testing, and which did not affect their daily life. On the other hand, two of the six subjects in the dexamethasone-untreated group had severe or profound SNHI and were obliged to use a hearing device. This finding might support the use of adjuvant dexamethasone therapy to prevent serious SNHI in PM.

Table VI. Differences Between First Hearing Test Within Six Weeks of Bacterial Meningitis and Present Evaluation

Groups	No difference	Improvement	Worsening	Total
1 (Dexamethasone untreated)	9	1*	1¤	11
2 (Dexamethasone treated)	10	1*	0	11
Total	19	2	1	22

*: Unilateral minimal improvement in SNHI.
¤: Unilateral worsening in SNHI from minimal to profound level.

The results of this study are consistent with a previously published prospective study organized in the same pediatric clinic about 10 years ago[9]. Kanra et al.[9] had compared placebo with dexamethasone in PM subjects for four years. Some of the patients included in that study also participated in the present study. They had reported, similar to this study, that unilateral or bilateral moderate or severe hearing impairment was less likely to occur in the group receiving dexamethasone for PM, although it was not statistically significant.

Richardson et al.[10] reported that incidence of reversible hearing loss was 10.5% after bacterial meningitis. Seventy-five percent of the subjects who had SNHI at admission regained normal hearing within 48 hours. In the literature, fluctuation of hearing tends to occur during the first 12 months after bacterial meningitis[11]. Since there are some articles reporting hearing loss 12 years[12] and 17 years[13] after bacterial meningitis, we investigated if there was any difference between initial hearing evaluation and the present testing.

Although 29 (52.7%) parents recalled a hearing evaluation after meningitis (within 6 weeks of meningitis), test results for only 22 (40%) were present in the related binders. We compared those findings with the present data, and found that the majority of subjects, 19 cases (86%), demonstrated no difference in hearing ability. Two of the subjects (9%) had minimal improvement in hearing. The remaining subject had experienced difficulty in hearing at the age of six, about two years after PM. Serial follow-up of the patient revealed unilaterally gradual worsening of SNHI as profound loss. The patient had commenced using a hearing aid device since the first years of primary school.

The hearing thresholds of the dexamethasone-treated group were almost always better than the dexamethasone-untreated group at each frequency. However, statistically significant differences occurred only at higher frequencies, which are barely involved in speech discrimination: 10,000 dB for both ears, and at 12,000 dB for the left ear. Although hearing impairment at higher frequencies has limited impact on daily life, this condition once again might support the use of dexamethasone in PM.

Dexamethasone therapy was used in patients of whom the majority were admitted to our emergency department as a first-line health care center; they had no history of previous antibiotic therapy and underwent immediate management. Therefore, we should consider a possible bias in this study in that the findings suggesting the use of dexamethasone might be affected by the late admission of the subjects in the first group (who did not receive steroid), since 60% had previous antibiotic therapy in another institution. Another bias involves the lack of clearly noted information in some binders for other factors that could influence outcome: days of illness preceding diagnosis, dose and duration of previous antibiotics, coma scoring at admission, and seizures lasting more than 24 hours, etc.

The beneficial effects of dexamethasone were first reported regarding subjects with Hib meningitis, but its salutary effects are believed to apply to PM as well[14,15]. Increased incidence in bacterial meningitis by highly-resistant pneumococcal strains has raised concern regarding the use of steroids[15,16] due to decreased penetration of antibiotics into the CSF. The lack of vaccination for pneumococcus in daily practice is obvious not only in developing countries but also developed nations for various reasons. Therefore, immunization for *Streptococcus pneumoniae* should be encouraged worldwide to catch-up a similar trend as with *Haemophilus influenzae* type B, which was once a major meningeal pathogen in early childhood.

In conclusion, dexamethasone has no statistically significant effect on hearing ability in PM subjects after a long-term follow-up. However, its use is still a good choice in the light of findings derived from the present study, in terms of preventing serious SNHI. In addition, hearing evaluation should be recommended for all patients as part of routine follow-up after bacterial meningitis for early identification and rehabilitation of hearing loss, which is essential for the acquisition of normal speech and language.

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