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ORIGINAL ARTICLE

Early Dexamethasone Treatment Enhances Hearing Preservation after Pneumococcal Meningitis: An Animal Study

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Objective: We aimed to investigate the effects of early and late dexamethasone treatment combined with antibiotics on hearing preservation on experimental rat pnemococcal meningitis model.

Materials and Methods: Thirty rats with confirmed diagnosis of meningitis after intracisternal S. pneumonia injection were randomly assigned to 3 groups. Animals in group 1 recieved intramuscular (im) ceftriaxone for 7 days, animals in group 2 recieved im dexamethasone on days 4-7 adjunct to im ceftriaxone treatment and animals in group 3 received im dexamethasone on days 1-4 adjunct to im ceftriaxone treatment. Hearing status of all rats were evaluated by auditory brainstem responses (ABR) on days 7 and 28 and categorized as normal hearing, moderate hearing loss, severe hearing loss and profound hearing loss.

Results: Right ear ABR results on day 7 showed statistically significant difference in hearing levels among the groups favoring steroid treatment ($p<0.03$). Left ear ABR results on day 7 showed no significant difference among the groups ($p>0.05$). Right and left ear ABR results on day 28 showed statistically significant difference in hearing levels among the groups favoring steroid treatment ($p<0.02$). The progression of hearing status among the categories between day 7 and 28 didn't show a significant difference among the groups ($p>0.05$).

Conclusions: Administration of dexamethasone, especially early in the course of the disease, concurrent with antibiotics will have otoprotective effects in individuals with pneumococcal meningitis.

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Meningitis is an inflammatory disease caused by a variety of microorganisms (bacteria, viruses, fungi, parasites) that has the potential to damage the meninx and the cerebral tissue. Bacterial meningitis (BM), despite early diagnosis and appropriate therapy, is associated with devastating mortality rates up to 30% particularly in children [1-4]. Permanent neurologic sequela including hearing loss (HL), mental retardation, learning impairment, sensorimotor deficits, seizures and cerebral palsy can be seen in 20% to 50% of pediatric patients [1-5]. HL is a common sequela of BM which is reported in 5% to 35% of cases, 37% of whom are affected bilaterally [6-11]. S. pneumonia meningitis is associated with the highest rate of postmeningitic HL, affecting up to 30% of those who survived the disease [1,6,12,13]. The inflammatory response caused by pneumococcal infection was blamed to produce auditory nerve and cochlear damage leading to cochlear function loss [1,6,7,10]. Frequently, labyrinthine ossification occurs which complicates the rehabilitation of HL with cochlear implant due to technical difficulties [6,10]. Furthermore, patients with labyrinthitis ossificans have poorer hearing outcomes with the cochlear implant [6]. Therefore, introduction of steroids, in addition to antibiotics, may protect against postmeningitic HL and labyrinthitis ossificans by inhibiting the inflammatory response [1-7]. Although many clinical studies support the effectiveness of adjunctive steroid treatment to prevent HL after pneumococcal meningitis [2-7,14], some

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studies oppose to this opinion [1,15-18]. A concensus recommendation regarding the adjunctive steroid treatment for pneumococcal meningitis was issued by van de Beek et al [14]. The aim of the present study was to evaluate the effects of early and late dexamethasone treatment combined with antibiotics on hearing preservation on experimental rat pnemococcal meningitis model.

Materials and Methods

Animals

Thirty healthy male Wistar albino rats with intact tympanic membranes weighing 180-260 grams were used in the study. Baseline auditory brainstem responses (ABRs) were obtained to rule out preexisting HL [19]. All rats were deeply anesthetized with intramuscular ketamine (50 mg/kg) and xylazine (10 mg/kg) and ABRs were measured with intradermal recording electrodes, insert earphones (Eartone 3A Insert Earphone) and click stimulation (Intelligent Hearing System, SmartEP). Rats that revealed wave V at 30 dB nHL were enrolled in the study. Experiments for this study was approved by the Animal Use Committee at Ondokuz Mayis University Medical Center.

Experimental Design

The rats that passed the ABR test were injected intracisternally with 0.1 ml saline containing 1.5x106 colony-forming units (CFU)/ml S. pneumonia (ATCC #6303). At 18 hour after injection, CSF was obtained from the cisterna magna of all animals to document infection. Meningitis was confirmed with the leukocyte count of 200/mm3 or higher on Thoma slide. Thirty animals were proven to have meningitis at 18 hour after bacterial inoculation. Rats were randomly assigned to 3 groups. In group 1 (Antibiotic only), 10 rats recieved intramuscular (im) ceftriaxone 100mg/kg/day for 7 days starting at 18 hr. In group 2 (Antibiotic + late dexamethasone), 10 rats recieved im ceftriaxone 100mg/kg/day for 7 days starting at 18 hr and im dexamethasone 0.5 mg/kg/day on days 4-7. In group 3 (Antibiotic + early dexamethasone), 10 rats recieved im ceftriaxone 100mg/kg/day for 7 days and im dexamethasone 0.5 mg/kg/day on days 1-4 starting at 18 hr. All rats in 3 groups underwent ABR testing on day 7 and day 28 (Tables 1-3).

Table 1. Right and Left ear ABR results in "Antibiotic Only" group on day 7 and 28

Rat number	Ear	Day 7 ABR results (dB)	Day 28 ABR results (dB)
1	R	NH	NH
	L	NH	SHL
2	R	SHL	SHL
	L	SHL	NH
3	R	SHL	NH
	L	MHL	SHL
4	R	MHL	SHL
	L	MHL	NH
5	R	NH	PHL
	L	MHL	MHL
6	R	NH	MHL
	L	MHL	MHL
7	R	SHL	SHL
	L	SHL	PHL
8	R	MHL	PHL
	L	NH	NH
9	R	NH	NH
	L	NH	PHL
10	R	PHL	PHL
	L	PHL	PHL

R; Right, L; Left, NH; Normal Hearing, MHL; Moderate Hearing Loss, SHL; Severe Hearing Loss, PHL; Profound Hearing Loss
Light gray highlighted ears: Better progression
Dark gray highlighted ears: Worse progression

ABR testing

Intelligent Hearing System SmartEP device, Ear-Tone 3A Insert Earphone and intradermal recording electrodes were used for ABR testing. All rats were deeply anesthetized with intramuscular ketamine (50 mg/kg) and xylazine (10 mg/kg) before day 7 and day 28 ABR measurements. Both ears were seperately tested by single-channel electrodes [19]. Intradermal electrodes were placed in the mastoid of the tested ear (active), at the vertex (reference) and in the cervical neck muscles (ground). Insert earphone was placed in the tested ear with an appropriate probe tip. ABR testing was done on prone position with alternate mode, 1,024 sweep, 19.3 rate and click stimulation.

Table 2. Right and Left ear ABR results in "Antibiotic + Late Dexamethasone" group on day 7 and 28

Rat number	Ear	Day 7 ABR results (dB)	Day 28 ABR results (dB)
1	R	PHL	PHL
	L	PHL	PHL
2	R	NH	NH
	L	NH	NH
3	R	PHL	PHL
	L	PHL	PHL
4	R	NH	NH
	L	MHL	NH
5	R	MHL	NH
	L	NH	NH
6	R	MHL	PHL
	L	MHL	PHL
7	R	NH	NH
	L	PHL	PHL
8	R	NH	NH
	L	MHL	NH
9	R	NH	NH
	L	NH	NH
10	R	NH	NH
	L	NH	NH

R; Right, L; Left, NH; Normal Hearing, MHL; Moderate Hearing Loss, SHL; Severe Hearing Loss, PHL; Profound Hearing Loss
Light gray highlighted ears: Better progression
Dark gray highlighted ears: Worse progression

Acoustic stimuli were presented at 30, 50 and 70 dB nHL. Wave 5 latency was solely measured, the other wave formations and wave 5 amplitude weren't evaluated. The hearing status of the rats were classified as "normal hearing" (presence of wave 5 at 30 dB nHL), "moderate hearing loss" (presence of wave 5 at 50 dB nHL), "severe hearing loss" (presence of wave 5 at 70 dB nHL) and "profound hearing loss" (absence of wave 5 at 70 dB nHL). The ABR measurements were conducted in a 2x2 m2 room with a noise level less than 45 dB SPL. The audiologist was blinded about the rat groups throughout the ABR measurements conducted on 2 different days.

Statistical analysis

Kendall's-tau-c test was used for statistical evaluation of the 3 rat groups since the measurement scale of hearing evaluation was staged in 4 different categories from "profound hearing loss" to "normal hearing". Hearing status progression between day 7 and 28 was evaluated by Chi-square test.

Table 3. Right and Left ear ABR results in "Antibiotic + Early Dexamethasone" group on day 7 and 28

Rat number	Ear	Day 7 ABR results (dB)	Day 28 ABR results (dB)
1	R	NH	NH
	L	NH	NH
2	R	MHL	NH
	L	MHL	NH
3	R	NH	NH
	L	MHL	MHL
4	R	NH	SHL
	L	NH	NH
5	R	MHL	NH
	L	PHL	MHL
6	R	NH	NH
	L	NH	NH
7	R	NH	NH
	L	NH	NH
8	R	NH	MHL
	L	MHL	MHL
9	R	NH	SHL
	L	NH	NH
10	R	NH	NH
	L	MHL	NH

R; Right, L; Left, NH; Normal Hearing, MHL; Moderate Hearing Loss, SHL; Severe Hearing Loss, PHL; Profound Hearing Loss
Light gray highlighted ears: Better progression
Dark gray highlighted ears: Worse progression

Results

Day 7 ABR evaluations

On day 7, the left ear ABR evaluations did not reveal a significant difference (Table 4). There were ears with normal hearing and profound hearing loss in all 3 groups. The distribution of ears in 3 groups among the staged hearing categories was balanced ($p>0.05$, Kendall's-tau-c test). The right ear ABR evaluations on day 7 showed a significant difference ($p<0.03$, Kendall's-tau-c test) favoring the Antibiotic+Early Dexamethasone (AB+Early Dex) group with regards to better hearing outcomes (Table 5). Eight ears in "AB+Early Dex" group (Group 3) had normal hearing whereas 6 and 4 ears had normal hearing in "AB+Late Dex" (Group 2) and "AB only" (Group 1) groups

respectively. No ear in "AB+Early Dex" group had either profound or severe HL.

Day 28 ABR evaluations

On day 28, the left ear ABR evaluations revealed a significant difference ($p<0.02$, Kendall's-tau-c test) favoring the "AB+Early Dex" group with regards to better hearing outcomes (Table 6). Seven ears in "AB+Early Dex" group had normal hearing whereas 6 and 3 ears had normal hearing in "AB+Late Dex" and "AB only" groups respectively. No ear in "AB+Early Dex" group had either profound or severe HL. The right ear ABR evaluations on day 28 showed a significant difference ($p<0.02$, Kendall's-tau-c test) favoring the "AB+Early Dex" group with regards to better hearing outcomes (Table 7). Fourteen ears (seven in each group) in "AB+Early Dex" and "AB+Late Dex" groups had normal hearing whereas only 3 ears had normal hearing in "AB only" group. The progression of hearing status between day 7 and 28 was evaluated in Table 8. Although the better or worse hearing status progression patterns between day 7 and 28 didn't show a statistically significant difference among the groups, 8 ears in "AB only" group showed worse progression whereas the number of ears that showed worse progression in "AB+Late Dex" and "AB+Early Dex" groups were 2 and 3 respectively. Similarly, 5 ears in "AB+Early Dex" group showed better progression between day 7 and 28 compared to 3 ears in each remaining group. Rats showing better and worse progression between two ABR evaluations were highlighted with yellow and red respectively (Tables 1-3).

Table 4. Day 7 Left Ear ABR Evaluations

	Group1 AB only	Group 2 AB+Late Dex	Group 3 AB+Early Dex
Dex			
Profound HL	1	3	1
Severe HL	2	0	0
Moderate HL	4	4	4
Normal Hearing	3	3	5
Total	10	10	10

HL; Hearing Loss, AB; Antibiotic, Dex; Dexamethasone
p>0.05, Kendall's-tau-c test

Table 5. Day 7 Left Ear ABR Evaluations

	Group1 AB only	Group 2 AB+Late Dex	Group 3 AB+Early Dex
Profound HL	1	2	0
Severe HL	3	0	0
Moderate HL	2	2	2
Normal Hearing	4	6	8
Total	10	10	10

HL; Hearing Loss, AB; Antibiotic, Dex; Dexamethasone
p>0.05, Kendall's-tau-c test

Table 6. Day 28 Left Ear ABR Evaluations

	Group1 AB only	Group 2 AB+Late Dex	Group 3 AB+Early Dex
Profound HL	3	4	0
Severe HL	2	0	0
Moderate HL	2	0	3
Normal Hearing	3	6	7
Total	10	10	10

HL; Hearing Loss, AB; Antibiotic, Dex; Dexamethasone
p>0.05, Kendall's-tau-c test

Table 7. Day 28 Left Ear ABR Evaluations

	Group1 AB only	Group 2 AB+Late Dex	Group 3 AB+Early Dex
Profound HL	3	3	0
Severe HL	3	0	2
Moderate HL	1	0	1
Normal Hearing	3	7	7
Total	10	10	10

HL; Hearing Loss, AB; Antibiotic, Dex; Dexamethasone
p>0.05, Kendall's-tau-c test

Table 8. Hearing status progression between day 7 and day 28

	Group1 AB only	Group 2 AB+Late Dex	Group 3 AB+Early Dex
Worse Progression	8	2	3
Better Progression	3	3	5
No Change	9	15	12
Total	20	20	20

Chi-Square test, p>0.05
HL; Hearing Loss, AB; Antibiotic, Dex; Dexamethasone

Discussion

Although the vaccination decreased the incidence of BM caused by S. pneumonia, it continues to be an

important pathogen with remarkable morbidity and mortality. Even with early diagnosis and institution of antibiotic treatment, acute pneumococcal meningitis has a mortality rate of 2.6% [6]. Almost a third of patients who survive the disease suffer from sensorineural HL, often bilaterally [1,6,12,13]. Host inflammatory response to the infection seems to be the cause of the cochlear damage [1,6,7,10]. Therefore, anti-inflammatory adjunct to antibiotic therapy can be postulated to reduce the HL associated with BM [1-7]. However, data from clinical trials have been conflicting [1-7,14-18]. Rappaport et al [5] studied the effects of dexamethasone and ketorolac adjunct to ampicillin treatment in the rabbit model and showed the protective role of anti-inflammatory drugs in reducing the incidence of HL associated with S. pneumonia meningitis, especially when the therapy is started early in the course of infection. Kim et al [6] showed that the spiral ganglion cell density in the basal turn was significantly less in animals which were treated with antibiotic only compared with the animals which were treated with antibiotic and dexamethasone in experimental gerbil pneumococcal meningitis model. In the present study, we investigated the effects of early and late dexamethasone administration adjunct to antibiotic therapy and quantified the hearing status as "normal hearing", "moderate HL", "severe HL", and "profound HL". The right ear ABR findings on day 7 favored the benefits of dexamethasone treatment especially if started early whereas the left ear ABR findings on day 7 revealed no difference among the groups. ABR findings on day 28 favored the otoprotective effects of dexamethasone treatment especially if started early in the course. On day 28, no ears in group 3 had profound HL and 14 ears out of 20 had normal hearing. In group 2, 13 ears out of 20 had normal hearing whereas 7 ears had profound HL. When changes in hearing outcomes were taken into consideration, no statistically significant difference was seen but 8 ears in group 1 had worse progression compared to 2 and 3 ears in group 2 and 3 respectively whereas 5 ears in group 3 had better progression compared to 3 ears in each remaining group. Our results support that HL associated with BM may have a fluctuating course and be unilateral or bilateral. On day 28, the number of "normal hearing" ears in "AB+Late Dex" and "AB+Early Dex" groups are 13 and 14 respectively whereas only 6 ears in "AB only" group had normal hearing. The major superiority of early versus late steroid administration is seen with the number of ears having profound HL. Six ears in "AB only" group and 7 ears in "AB+Late Dex" group had profound HL compared to no ear with profound HL in "AB+Early Dex" group. We suggest , based on our experimental rat model, that early administration of dexamethasone concurrent with antibiotics will have otoprotective effects in individuals with pneumococcal meningitis.

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