Pediatr Infect Dis J, 8:848-851 1989
0891 3668/89/$02.00/0
Copyright © 1989 by Williams & Wilkins

Vol. 8, No. 12
Printed in U.S.A.

Dexamethasone treatment for bacterial meningitis in children and adults

NABIL I. GIRGIS, MBBCH, ZOHEIR FARID, FACP, DTM&H, ISIS A. MIKHAIL, PHD, IBRAHIM FARRAG, MBBCH, YEHIA SULTAN, MBBCH AND MICHAEL E. KILPATRICK, MD

Four hundred twenty-nine patients with bacterial meningitis were assigned on a nonselective alternating basis into one of two therapeutic regimens. Patients in Group I received dexamethasone in addition to standard antibacterial chemotherapy of ampicillin and chloramphenicol whereas those in Group II received antibacterial chemotherapy alone. Dexamethasone was given intramuscularly (8 mg to children younger than 12 years and 12 mg to adults every 12 hours for 3 days). Both treatment groups were comparable with regard to age, sex, duration of symptoms and state of consciousness at the time of hospitalization.

A significant reduction in the case fatality rate ($P < 0.01$) was observed in patients with pneumococcal meningitis receiving dexamethasone; only 7 of 52 patients died compared with 22 of 54 patients not receiving dexamethasone. A reduction in the overall neurologic sequelae (hearing impairment and paresis) was observed in patients receiving dexamethasone. This reduction was significant only in patients with *Streptococcus pneumoniae* meningitis; none of the 45 surviving patients receiving steroids had hearing loss whereas 4 of 32 patients not receiving dexamethasone had severe hearing loss ($P < 0.05$). No significant difference was observed between the two groups with regard to time for patients to become afebrile or to regain consciousness or in the mean admission and 24- to 36-hour cerebrospinal fluid leukocyte count, glucose or protein content.

INTRODUCTION

Despite the introduction of newer and more potent antibacterial agents, the mortality from bacterial meningitis is still high and age-dependent, ranging from 5 to 10% for *Neisseria meningitidis* and 5 to 30% for *Haemophilus influenzae* and *Streptococcus pneumoniae*.[1, 2] Permanent neurologic sequelae occur in 10 to 20% of survivors.[3, 4] Several factors are involved in the pathophysiologic mechanisms by which destruction and dysfunction of the brain cells occur as a result of the inflammatory process.[5] Bacteria gain access into the cerebrospinal fluid (CSF) where logarithmic multiplication and bacterial destruction occurs. The cell wall components stimulate the production of cytokines such as interleukin 1 and cachectin (tumor necrosis factor) in the central nervous system.[6, 7] Both these factors increase the disruption and dysfunction of the blood-brain barrier composed of cerebral capillary endothelial cells,[5] increasing passage of serum proteins and migration of polymorphonuclear leukocytes from the blood into the CSF.[8] Adhesiveness of the circulating neutrophils to the capillary endothelium wall is increased, probably mediated by chemotactic factors.[9] The increase in breakdown of bacterial cell walls and release of endotoxin and other active components causes thrombosis and vasculitis of the blood vessels leading to areas of necrosis in the brain tissue. This increases cytotoxic and vasogenic brain edema and obstruction of the CSF pathways, leading to intracranial hypertension.[6, 10]

Dexamethasone therapy in experimental animals reduces significantly the production of interleukin 1 and tumor necrosis factor activity, neutrophil adhesiveness, CSF lactate concentrations and prostaglandin E_2 concentrations which appear to play a role in disruption and dysfunction of the blood-brain barrier and in promoting meningeal inflammation. Dexamethasone therapy in this model reduces inflammation in CSF and reduces brain edema and intracranial pressure.[9, 10-13]

Results of clinical studies to evaluate the efficacy of corticosteroids in meningitis have been inconclusive and controversial.[14-16] Only recently has dexamethasone been shown to be of benefit in infants and children with bacterial meningitis.[17-19]

The aim of this study was to evaluate the use of dexamethasone administered in conjunction with antibacterial chemotherapy in the treatment of meningitis in children and adults. The study was started in

Accepted for publication Sept. 11, 1989.
From the Abbassia Fever Hospital, United States Naval Medical Research Unit No. 3 and the Egyptian Ministry of Health, Cairo, Egypt.
Key words: Dexamethasone, bacterial meningitis.
Address for reprints: Research Publication Branch, NAMRU-3, FPO New York 09527-1600.

1983 in Cairo, Egypt, at the joint Abbassia Fever Hospital/Naval Medical Research Unit No. 3 (NAMRU-3) meningitis ward. This hospital is a referral center for all febrile patients from the greater Cairo area (population 10 million).

PATIENTS AND METHODS

This was an open prospective study. Patients of all ages and both sexes who presented with signs and symptoms of acute bacterial meningitis were assigned according to a predesigned randomization chart on a nonselective alternating basis into one of two therapeutic regimens. One received dexamethasone and ampicillin and chloramphenicol and the other received ampicillin and chloramphenicol only. This antibiotic regimen is the routine therapy recommended by the Ministry of Health for treating children and adults with meningitis. The trial was approved by the Egyptian Ministry of Health and the NAMRU-3 Committee for the Protection of Human Subjects. Informed consent was obtained from the patient's parents or guardians before enrollment into the study.

A diagnostic lumbar puncture was performed upon admission and the CSF was examined for total and differential leukocyte count, glucose and protein concentrations and bacteriologically by Gram-stained smear and culture. Blood was drawn for complete blood count, culture, glucose, blood urea nitrogen, alanine aminotransferase, aspartate aminotransferase and creatinine concentrations. Repeat CSF and blood examination were carried out after 24 to 36 hours and again 7 days after initiation of therapy.

Ampicillin (160 mg/kg/day in four divided doses) and chloramphenicol (100 mg/kg/day in four divided doses) were administered intramuscularly to children and adults. Patients in Group I received dexamethasone which was administered concomitantly with the first dose of antibiotic (8 mg to children younger than 12 years and 12 mg to adults every 12 hours for 3 days). Antibacterial chemotherapy was stopped in both groups after 8 days, except in 10 patients in Group I and 15 in Group II who were still febrile or in whom the CSF examination was still abnormal. In these patients therapy was extended for 2 to 3 days.

Patients were examined ophthalmologically including fundus examination and neurologically twice weekly during their hospitalization, then once monthly during the follow-up period of 6 months. Estimation of hearing was performed once patients were alert enough and then monthly for 6 months. The definition of hearing loss followed the 1965 American Society of Audiology guidelines. Hearing loss was graded as mild if the loss was from 15 to 80 dB, moderate from 80 to 110 dB and severe if greater than 110 dB. An audiometer (Beltone®) was used to evaluate adults and larger children. For smaller children who could not be measured by this instrument, hearing was tested by whispered voice, conversational voice and drum rattles with a pressure sound level meter (SPL) placed near the ear to determine the decibels of SPL (A scale) presented. If the whispered voice was not heard hearing loss was considered to be more than 40 dB SPL (mild). If the conversational voice was not heard hearing loss was more then 80 dB SPL (moderate), and if drum rattles were not heard hearing loss was more than 110 dB SPL (severe). Ophthalmologic and ear, nose and throat examinations were performed by the ophthalmology and ear, nose and throat services.

Statistical evaluation was carried out using a test for two proportions from independent groups. Fisher's exact test was used to assess differences in proportions and the Student's t test was used for numerical variables.

RESULTS

Of the 470 patients enrolled into the study according to the protocol, only 429 from whom organisms were isolated from the CSF or were present on Gram-stained smear of the CSF were included in the final analysis (Table 1). The remaining 41 patients were excluded because the CSF and blood cultures were sterile and no organism could be seen on Gram-stained films of the CSF; 15 received steroids and 1 died; 26 did not receive steroids and 1 died. These patients gave histories of having received high doses of appropriate antibiotics before hospitalization, whereas patients in whom organisms were seen or cultured usually reported having taken one or two doses of inadequate antibiotics. The most frequently used antibiotics before hospitalization were ampicillin, tetracycline or trimethoprim/sulfamethoxazole. Of the 429 patients included in the final analysis, there were 278 males and 151 females, ranging in age from 3 months to 60 years (mean, 12.5 years). Two hundred ten patients received antibiotics plus dexamethasone (Group I) and 219 received antibiotics alone (Group II). Patients in both groups were comparable in age, sex, duration of symptoms before hospitalization and state of consciousness at the time of hospitalization (1% alert, 35% drowsy and 64% comatose) (Table 2). One hundred thirty-three patients in Group I and 140 in Group II were comatose. The delay between the onset of symptoms and admission (Table 2) contributed to the morbidity at admission. One hundred seventy-eight patients in Group I and 192 in Group II received inadequate treatment for 3 to 5 days before admission to the hospital.

The case fatality rate was significantly lowered in patients receiving dexamethasone; 20 of 210 patients treated with antibiotics and dexamethasone died compared with 42 of 219 receiving antibiotics alone ($P < 0.01$). This reduction was significantly different for patients with *S. pneumoniae* meningitis; 7 of 52 (13.5%) for Group I died compared with 22 of 54

TABLE 1. Causative organism in 429 patients with bacterial meningitis

	Treatment					
	Group I[a]			Group II[b]		
	Total	Culture	Gram-stained smear	Total	Culture	Gram-stained smear
Neisseria meningitidis	132	90	42	135	85	50
Streptococcus pneumoniae	52	42	10	54	46	8
Haemophilus influenzae	26	20	6	30	22	8
	210	152	58	219	153	66

[a] Treated with dexamethasone, ampicillin and chloramphenicol.
[b] Treated with ampicillin and chloramphenicol.

TABLE 2. Clinical presentation of patients with meningitis[a]

	Group I[b]	Group II[c]
Sex		
Male	143	135
Female	67	84
Age (years) (mean ± SD)	13.85 ± 8.58	12.92 ± 8.75
Duration of symptoms prior to admission (days)		
<2	32 (4)[d]	23 (4)
2–4	128 (8)	152 (24)
>4	50 (8)	44 (14)
State of consciousness on hospitalization		
Alert	3 (0)	3 (0)
Drowsy	74 (2)	76 (6)
Comatose	133 (18)	140 (36)

[a] There were no statistically significant differences between the two groups.
[b] Treated with dexamethasone, ampicillin and chloramphenicol.
[c] Treated with ampicillin and chloramphenicol.
[d] Numbers in parentheses, number of deaths.

(40.7%) for Group II ($P < 0.002$) (Table 3). The permanent neurologic sequelae seen on discharge and during the 6-month follow-up period were reduced in patients treated with dexamethasone (Table 4), but significant benefit occurred only in patients with *S. pneumoniae* meningitis where none of the 45 surviving patients in Group I developed hearing loss whereas 4 of 32 in Group II became deaf ($P < 0.05$) (Table 4). Audiometric evaluations could not be done in children younger than 4 years of age because responses could not be determined. The mean time for patients to become fully alert and afebrile was similar in both groups: 5.60 ± 2.80 days to become fully alert in Group I compared with 5.25 ± 2.35 days in Group II ($P > 0.05$) and 4.65 ± 2.55 days to become afebrile in Group I compared to 4.75 ± 2.45 days in Group II ($P > 0.05$). There were no significant differences in the mean admission and 24- to 36-hour CSF leukocyte count, glucose or protein concentrations between the two groups (Table 5).

DISCUSSION

The results of this study in children and adults are in agreement with the recently published studies in children where dexamethasone was useful in reducing the neurologic sequelae (especially bilateral moderate

TABLE 3. Mortality and mental status of patients with bacterial meningitis

Organism	Age (Years)				Duration of Symptoms before Hospitalization (Days)		
	<6	6–12	13–25	>25	<2	2–4	>4
Neisseria meningitidis							
Group I[a]							
Total no.	21	62	31	18	26	86	20
No. comatose	16	25	15	10	7	47	12
No. drowsy	5	35	15	8	19	36	8
No. alert	0	2	1	0	0	3	0
No. deaths	2	1	1	2	2	3	1
Group II[b]							
Total no.	23	53	39	20	16	109	10
No. comatose	17	35	20	15	8	70	9
No. drowsy	6	15	19	5	8	36	1
No. alert	0	3	0	0	0	3	0
No. deaths	3	1	2	4	1	8	1
Streptococcus pneumoniae							
Group I							
Total no.	18	15	4	15	5	32	15
No. comatose	15	14	2	10	2	26	13
No. drowsy	3	1	2	5	3	6	2
No. deaths	3	2	1	1	2	2	3
Group II							
Total no.	22	12	8	12	7	34	13
No. comatose	16	11	3	7	3	24	10
No. drowsy	6	1	5	5	4	10	3
No. deaths	8	2	3	9	2	11	9
Haemophilus influenzae							
Group I							
Total no.	26				1	10	15
No. comatose	16				1	6	9
No. drowsy	10				0	4	6
No. deaths	7				0	3	4
Group II							
Total no.	30				0	9	21
No. comatose	16				0	8	8
No. drowsy	14				0	1	13
No. deaths	10				0	5	5

[a] Treated with dexamethasone, ampicillin and chloramphenicol.
[b] Treated with ampicillin and chloramphenicol.

TABLE 4. Permanent sequelae in the 367 surviving patients with bacterial meningitis

	Group I[a]		Group II[b]	
	No. living	No. with sequelae	No. living	No. with sequelae
Neisseria meningitidis	126	4[c]	125	4[d]
Streptococcus pneumoniae	45	0	32	4[e]
Haemophilus influenzae	19	0[f]	20	0[f]
	190	4	177	8

[a] Treated with dexamethasone, ampicillin and chloramphenicol.
[b] Treated with ampicillin and chloramphenicol.
[c] 1 hemiparesis, 1 unilateral severe hearing loss, 2 bilateral severe hearing loss.
[d] 2 hemiparesis, 1 unilateral severe hearing loss, 1 bilateral severe hearing loss.
[e] 4 bilateral severe hearing loss, $P < 0.05$.
[f] Hearing could not be properly evaluated because of age (see text).

TABLE 5. Cerebrospinal fluid findings on hospital admission and after 24 to 36 hours of therapy

CSF Finding	Dexamethasone and Antibiotics		Antibiotics Only	
	Admission	24–36 hours	Admission	24–36 hours
Leukocytes (cells/mm³)	24 000 ± 15 200[a]	3180 ± 2800	20 500 ± 17 300	4100 ± 8200
Glucose (mg/dl)	12.5 ± 10.1	22.2 ± 17.1	18.2 ± 14.3	35.3 ± 26.5
Protein (mg/dl)	310 ± 214	295 ± 228	270 ± 150	250 ± 170

[a] Mean ± SD

or greater hearing loss) in patients with meningitis.[19] We noted a significant decrease in the overall case fatality rate in patients with pneumococcal meningitis receiving dexamethasone ($P < 0.002$). This might be a result of the fact that dexamethasone prevents the severe pathologic lesions that occur with pneumococcal meningitis and cause leptomeningeal vasculitis of the venules, capillaries and arterioles with fibrin clot occlusion of the vessels resulting in necrosis and edema of brain tissue.[20]

Dexamethasone also significantly reduced the incidence of hearing loss in patients with pneumococcal meningitis but not in those with meningococcal meningitis. This may be because the course of the disease and the pathologic damage in patients with *N. meningitidis* was less severe and the damage to the cochlear and nerve endings occurred before hospitalization. We previously reported that hearing loss was directly related to the duration of symptoms before initiation of therapy[21] and that the use of dexamethasone in patients with tuberculous meningitis reduced the ocular complications but did not cure the irreversibly damaged optic nerves.[22] Lebel et al.[17] found that dexamethasone reduced hearing loss in children with *H. influenzae* meningitis. We were unable to evaluate hearing loss in our children with *H. influenzae* because they were too young for conventional audiometric evaluation and we did not have brainstem-evoked response audiometry available for use.

Lebel et al.[17, 18] found a significant reduction in the CSF leukocytes and an increase in glucose content 24 hours after initiation of antibiotic and steroid therapy. We did not detect these changes. This may be because most of our patients were usually treated before hospitalization[23] and because our follow-up examination was performed approximately 24 hours later than that in the Dallas patients.

From our study and those recently published in children[17–19] it appears that dexamethasone treatment improves outcome as demonstrated by reduced case-fatality rates, particularly in pneumococcal meningitis, and by reduced incidence of neurologic sequelae, especially hearing loss. We believe dexamethasone should be considered for treatment of patients with bacterial meningitis.

ACKNOWLEDGMENTS

This was supported by the United States Naval Medical Research and Development Command, Bethesda, MD, Work Unit No. 3M464758D849.BH.341. The opinions and assertions contained herein are the private ones of the authors and are not to be construed as official or reflecting the views of the Navy Department, the Department of Defense or the United States Government or the Egyptian Ministry of Health.

The authors wish to thank Dr. L. Bourgeois and Dr. S. Bassily for their helpful suggestions and guidance during the project, Dr. E. Fox for helping in the statistical analysis and Ms. Magda Erian for coordinating the laboratory studies and outpatient care.

REFERENCES

1. Wong VK, Hitchcock W, Mason WH. Meningococcal infections in children: a review of 100 cases. Pediatr Infect Dis J 1989;8:224–7.
2. McCracken GH Jr. Management of bacterial meningitis in infants and children: current status and future prospects. Am J Med 1984;76:215–23.
3. Greenwood BM, Bradley AK, Smith AW, Wall RA. Mortality from meningococcal disease during an epidemic in The Gambia, West Africa. Trans Soc Trop Med Hyg 1978;81:536–8.
4. Klein JO, Feigin RD, McCracken GH Jr. Report of the task force on the diagnosis and management of meningitis. Pediatrics 1986;78:959–82.
5. Täuber MG, Sande MA. Principles in the treatment of bacterial meningitis. Am J Med 1984;224–30.
6. Sande MA, Scheld WM, McCracken GH Jr. Summary of a workshop: pathophysiology of bacterial meningitis—implications for new management strategies. Pediatr Infect Dis J 1987;6:1167–71.
7. Moustafa MM, Lebel MH, Ramilo O, et al. Correlation of interleukin-1-beta and cachectin concentrations in cerebrospinal fluid and outcome from bacterial meningitis. J Pediatr 1989;115:208–13.
8. Zwahlen A, Nydegger UE, Vaudaux P, Lambert PH, Waldvogel FA. Complement-mediated opsonic activity in normal and infected human cerebrospinal fluid: early response during bacterial meningitis. J Infect Dis 1982;145:635–46.
9. Nolan CM, McAllister CK, Walter E, Beaty HN. Experimental pneumococcal meningitis: IV. The effect of methylprednisolone on meningeal inflammation. J Lab Clin Med 1978;91:979–88.
10. Täuber MG, Khayam-Bashi H, Sande MA. Effects of ampicillin and corticosteroids on brain water content, cerebrospinal fluid pressure, and cerebrospinal fluid lactate levels in experimental pneumococcal meningitis. J Infect Dis 1985;151:528–34.
11. Täuber MG, Brooks-Fournier RA, Sande MA. Experimental models of CNS infection: contributions to concepts of disease and treatment. Neurol Clin 1986;4:249–64.
12. Fishman RA. Steroids in the treatment of brain edema. N Engl J Med 1982;306:359–60.
13. Syrogiannopoulos GA, Olsen KD, Reisch JS, McCracken GH Jr. Dexamethasone in the treatment of experimental *Haemophilus influenzae* type b meningitis. J Infect Dis 1987: 155:213–9.
14. Bademosi O, Osuntokun BO. Prednisone in the treatment of pneumococcal meningitis. Trop Geogr Med 1979;31:53–6.
15. Belsey MA, Hofpauir CW, Smith MH. Dexamethasone in the treatment of acute bacterial meningitis: the effect of study design on the interpretation of result. Pediatrics 1969;44:503–15.
16. Badly JL, Passos J. Deametasona no tratamento da meningite meningococica. Rev Paul Med 1986;104:61–5.
17. Lebel MH, Freij BJ, Syroglannopoulos GA, et al. Dexamethasone therapy for bacterial meningitis: results of two double-blind, placebo-controlled trials. N Engl J Med 1988;3:964–71.
18. Lebel MH, Hoyt MJ, Waagner DC, Rollins NK, Finitzo T, McCracken GH Jr. Magnetic resonance imaging and dexamethasone therapy for bacterial meningitis. Am J Dis Child 1989;143:301–6.
19. McCracken GH Jr, Lebel MH. Dexamethasone therapy for bacterial meningitis in infants and children [Editorial]. Am J Dis Child 1989;143:287–9.
20. Dickson JG, Yassin MW. Meningeal vascular thrombosis and inflammation in pneumococcal meningitis. J Egypt Pub Health Assoc 1969;44:350–5.
21. Habib RG, Girgis NI, Yassin MW, Laughlin LW, Sippel JE, Edman DC. Hearing impairment in meningococcal meningitis. Scand J Infect Dis 1979;11:121–3.
22. Girgis NI, Farid Z, Hanna LS, Yassin MW, Wallace CK. The use of dexamethasone in preventing ocular complications in TB meningitis. Trans R Soc Trop Med Hyg 1983;77:658–9.
23. Kilpatrick ME, Mikhail IA, Girgis NI. Negative cultures of cerebrospinal fluid in partially treated bacterial meningitis. Trop Geogr Med 1987;39:345–9.