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Dexamethasone in Vietnamese Adolescents and Adults with Bacterial Meningitis

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ABSTRACT

BACKGROUND

It is uncertain whether all adults with bacterial meningitis benefit from treatment with adjunctive dexamethasone.

METHODS

We conducted a randomized, double-blind, placebo-controlled trial of dexamethasone in 435 patients over the age of 14 years who had suspected bacterial meningitis. The goal was to determine whether dexamethasone reduced the risk of death at 1 month and the risk of death or disability at 6 months.

RESULTS

A total of 217 patients were assigned to the dexamethasone group, and 218 to the placebo group. Bacterial meningitis was confirmed in 300 patients (69.0%), probable meningitis was diagnosed in 123 patients (28.3%), and an alternative diagnosis was made in 12 patients (2.8%). An intention-to-treat analysis of all the patients showed that dexamethasone was not associated with a significant reduction in the risk of death at 1 month (relative risk, 0.79; 95% confidence interval [CI], 0.45 to 1.39) or the risk of death or disability at 6 months (odds ratio, 0.74; 95% CI, 0.47 to 1.17). In patients with confirmed bacterial meningitis, however, there was a significant reduction in the risk of death at 1 month (relative risk, 0.43; 95% CI, 0.20 to 0.94) and in the risk of death or disability at 6 months (odds ratio, 0.56; 95% CI, 0.32 to 0.98). These effects were not found in patients with probable bacterial meningitis. Results of multivariate analysis indicated that dexamethasone treatment for patients with probable bacterial meningitis was significantly associated with an increased risk of death at 1 month, an observation that may be explained by cases of tuberculous meningitis in the treatment group.

CONCLUSIONS

Dexamethasone does not improve the outcome in all adolescents and adults with suspected bacterial meningitis; a beneficial effect appears to be confined to patients with microbiologically proven disease, including those who have received prior treatment with antibiotics. (Current Controlled Trials number, ISRCTN42986828.)

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PYOGENIC BACTERIAL MENINGITIS HAS neurologic sequelae or is fatal in 30% of affected patients.¹ Animal models of the disease suggest that the subarachnoid inflammatory response contributes to morbidity and mortality^{2,3} and that corticosteroids may improve the outcome by attenuating this response. However, confirming this effect in humans has proved difficult.⁴ We conducted a double-blind, placebo-controlled trial in Vietnam to determine whether adjunctive dexamethasone improves the outcome in adolescents and adults with bacterial meningitis.

A meta-analysis of randomized, controlled trials of corticosteroids for bacterial meningitis that were reported between 1966 and 2001 concluded that corticosteroids reduced the rates of death, neurologic sequelae, and hearing loss in children, but there were too few data on adults to confirm an effect.⁵ In 2002, two studies with conflicting results were published. The first, involving 598 Malawian children,⁶ showed that dexamethasone had no effect on the rates of death or neurologic sequelae. The second, involving 300 European adults, showed that fewer patients in the dexamethasone group died or were disabled as compared with the placebo group.⁷ A subsequent meta-analysis of five trials involving 632 adults showed that the use of adjunctive corticosteroids was associated with a reduction in the rates of death and sequelae, but the results were heavily influenced by the European trial, making it difficult to derive treatment recommendations for patients in different settings.⁸

METHODS

STUDY SETTING AND PARTICIPANTS

We recruited study participants from the Hospital for Tropical Diseases in Ho Chi Minh City, Vietnam. Patients older than 14 years with suspected bacterial meningitis were eligible to enter the study. Inclusion criteria were clinical evidence of meningitis (defined as nuchal rigidity, with elevations in the white-cell count and protein concentration in the cerebrospinal fluid) and at least one of the following: bacteria detected in cerebrospinal fluid by Gram's or acridine orange stain; a positive cerebrospinal fluid latex agglutination test (Wellcogen, Remel Europe); pathogenic bacteria cultured from either the blood or the cerebrospinal fluid; or a clinical history of less than 7 days of illness, with a cloudy cerebrospinal fluid, a white-cell count with more than 60% neutro-

phils, and a ratio of cerebrospinal fluid to blood glucose that was less than 50%. Patients were excluded from the study if they were in the first trimester of pregnancy, there was evidence of active pulmonary tuberculosis, the attending physician believed corticosteroids were contraindicated, or consent from either the patient or a family member was not obtained. Prior treatment with antibiotics was not a criterion for exclusion.

At the time of discharge from the hospital or death, patients were classified as having definite bacterial meningitis if bacteria were detected in the cerebrospinal fluid or cultured from the cerebrospinal fluid or blood. They were classified as having probable meningitis if bacteria were neither detected nor cultured, but there was no alternative diagnosis.

The ethics committee of the Hospital for Tropical Diseases approved the study protocol. Oral informed consent to participate in the study was obtained from all patients or their relatives.

LABORATORY STUDIES

Lumbar punctures were performed at presentation. Cerebrospinal fluid specimens were stained and cultured for bacteria with the use of standard methods. Drug-susceptibility tests were performed by means of standard methods, and resistance was confirmed with the Etest (AB-Biodisk). All patients were tested for antibodies to the human immunodeficiency virus (or HIV).

TREATMENT

Patients were randomly assigned to receive intravenous dexamethasone sodium phosphate, 0.4 mg per kilogram of body weight, every 12 hours for 4 days, or placebo. The study medication was given 15 minutes before the administration of antibiotics, although some patients may have had prior antibiotic treatment. A computer-generated sequence of random numbers was used to assign treatment in blocks of 100 patients. If a patient met the entry criteria, the attending physician instructed a nurse to open a numbered envelope containing instructions to give either active drug or placebo. To maintain blinding, a separate team of nurses, who were not otherwise involved in the care of the study patients, opened the envelopes and gave the injections. All patients, the physicians who enrolled them, and study investigators were unaware of the treatment assignments until the last patient had completed follow-up.

All patients were treated with ceftriaxone (2 g

given intravenously every 12 hours) for 10 to 14 days. Antibiotic treatment could be altered at the discretion of the attending physician. The attending physicians were responsible for enrolling the patients and recording the clinical data in individual study notes.

OUTCOME ASSESSMENT

The primary outcome was death 1 month after randomization. Secondary outcomes were death at 6 months, disability at 1 and 6 months, and hearing loss at 1 and 6 months. Disability was assessed with the use of the modified Rankin scale, on which a score of 0 indicates no symptoms; 1, minor symptoms not interfering with lifestyle; 2, symptoms that may restrict lifestyle but do not impede independent living; 3, symptoms that restrict lifestyle and interfere with independent living; 4, symptoms that clearly prevent independent living, although constant care and attention are not required; and 5, symptoms that result in complete dependence on others, requiring constant help day and night. Classification of the outcome as full recovery (a Rankin score of 0), mild sequelae (a score of 1 or 2), and severe disability (a score of 3, 4, or 5) was defined before the start of the trial. Hearing was assessed by means of audiometry. Deafness was defined as failure to register sounds of 80 dB or less.

STATISTICAL ANALYSIS

The mortality from microbiologically confirmed bacterial meningitis among adults at the hospital before the study (when corticosteroids were not administered) was 25%. We calculated that 150 patients with definite bacterial meningitis would be required in each treatment group to provide at least 80% power to detect a reduction in mortality from 25% to 12.5%, with a significance level of 0.05.

Data analysis followed a prespecified plan unless otherwise stated. Kaplan–Meier estimates of survival in the two study groups were compared with the use of the log-rank test. Data on patients who were lost to follow-up were censored at the time of the last recorded outcome. The relative risk of death between the treatment groups was calculated by means of Cox regression. A test of interaction with treatment was used to examine heterogeneity in treatment effect among subgroups of patients. Prespecified subgroup analysis compared the primary outcomes in participants grouped according to the diagnosis (definite vs. probable bacterial meningitis), sex, age (≤ 50 years

or >50 years), prior antibiotic treatment (yes or no), and the major pathogen group (gram-positive or gram-negative bacteria, *Streptococcus suis*, or *S. pneumoniae*). A multivariate Cox regression model, with a forward variable-selection procedure, was constructed to identify independent predictors of death during the first month.

Analysis of secondary outcomes, comparing death or severe disability, hearing loss, and adverse events after 6 months, was performed with the chi-square test, with odds ratios calculated by means of logistic regression. The last recorded disability score was obtained as the 6-month score for patients who did not complete follow-up. All analyses were performed with SPSS (Microsoft) and Stata (StataCorp) software. All reported P values are two-sided.

The data monitoring and safety committee reviewed the results of the study after the first 50 patients had been enrolled. The predefined criterion for stopping the trial early was a difference of more than 3 SD between the proportions

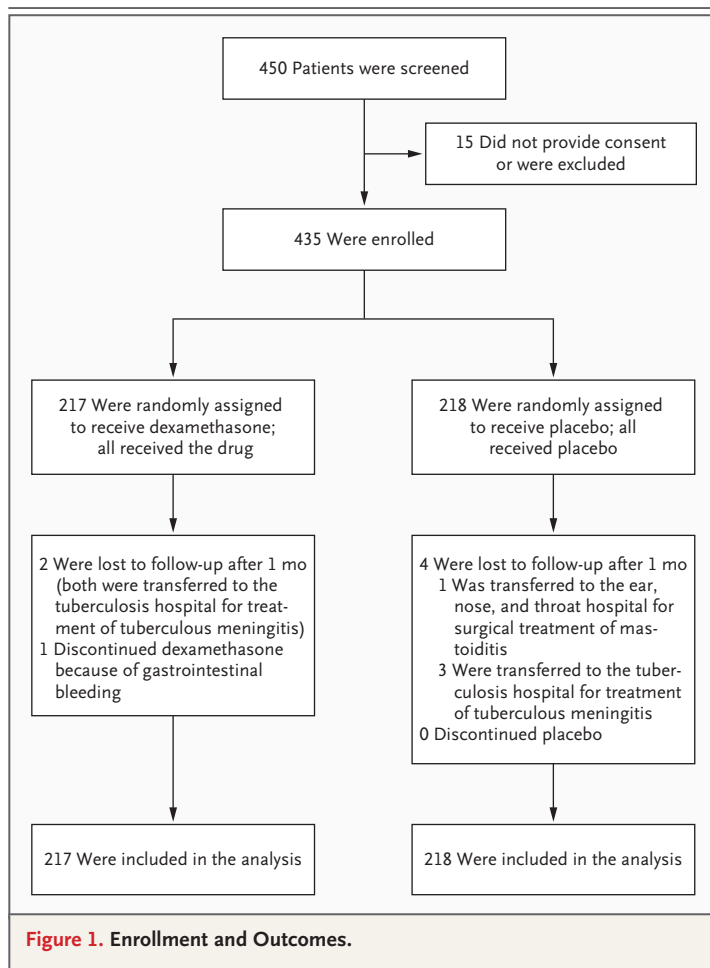


Figure 1. Enrollment and Outcomes.

of patients who died in the two groups; the trial was not stopped early.

RESULTS

CHARACTERISTICS OF THE PATIENTS

Between November 1996 and June 2005, a total of 435 patients were randomly assigned to receive dexamethasone (217 patients) or placebo (218) (Fig. 1). Definite bacterial meningitis was confirmed in 300 patients (69.0%), of whom 143 re-

ceived dexamethasone and 157 received placebo. Probable meningitis was diagnosed in 123 patients (28.3%), and an alternative diagnosis was made in 12 patients (2.8%) (Table 1). *Mycobacterium tuberculosis* was isolated from a cerebrospinal fluid culture in nine patients (four received dexamethasone, and five placebo), and *Cryptococcus neoformans* was isolated from one patient, who was given dexamethasone. Eosinophilic meningitis was diagnosed in two patients, both given placebo, on the basis of high proportions of eosinophils (>30%)

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Dexamethasone	Placebo
Age		
No. of patients	217	218
Median — yr	42	41
Range — yr	15–89	15–91
Male sex — no./total no. (%)	165/217 (76.0)	152/218 (69.7)
Duration of illness		
No. of patients	217	218
Median — days	4	3
Range — days	1–30	1–21
Prior antibiotic therapy — no./total no. (%)	139/217 (64.1)	128/218 (58.7)
Glasgow Coma Scale score†		
No. of patients	217	218
Median	13	13
Range	3–15	3–15
Rash — no./total no. (%)	23/213 (10.8)	19/215 (8.8)
Cranial-nerve palsy — no./total no. (%)	16/209 (7.7)	19/213 (8.9)
Hemiparesis — no./total no. (%)	23/201 (11.4)	13/200 (6.5)
Peripheral-blood white-cell count		
No. of patients	211	211
Median — per mm ³	16,000	17,200
Range — per mm ³	3600–80,000	2100–57,000
Pathogen cultured from blood — no./total no. (%)	66/217 (30.4)	62/218 (28.4)
HIV infection — no./total no. (%)	2/215 (0.9)	1/215 (0.5)
CSF opening pressure		
No. of patients	168	177
Median — cm	20	20
Range — cm	0–55	0–41
CSF total white-cell count		
No. of patients	216	217
Median — per mm ³	2970	2800
Range — per mm ³	1–30,000	35–64,000

Table 1. (Continued.)		
Characteristic	Dexamethasone	Placebo
CSF total protein		
No. of patients	214	210
Median — mg/dl	229	236
Range — mg/dl	20–1518	30–1460
Ratio of CSF glucose to plasma glucose		
No. of patients	213	218
Median	0.19	0.19
Range	0.004–0.71	0.001–0.68
Diagnosis — no./total no. (%)		
Definite bacterial meningitis	143/217 (65.9)	157/218 (72.0)
Probable bacterial meningitis	69/217 (31.8)	54/218 (24.8)
Other (not bacterial meningitis)‡	5/217 (2.3)	7/218 (3.2)
Pathogen cultured from CSF — no./total no. (%)		
<i>Streptococcus suis</i>	60/216 (27.7)	56/218 (25.7)
<i>S. pneumoniae</i>	26/216 (12.0)	29/218 (13.3)
Streptococcus species§	6/216 (2.8)	12/218 (5.5)
<i>Staphylococcus aureus</i>	3/216 (1.4)	6/218 (2.8)
Coagulase-negative staphylococcus	0	1/218 (0.5)
<i>Neisseria meningitidis</i>	9/216 (4.1)	10/218 (4.6)
<i>Haemophilus influenzae</i>	1/216 (0.5)	6/218 (2.8)
Klebsiella species	7/216 (3.2)	3/218 (1.4)
<i>Escherichia coli</i>	6/216 (2.8)	3/218 (1.4)
Other gram-negative bacteria¶	2/216 (0.9)	2/218 (0.9)
Bacteria seen in CSF but not cultured — no./total no. (%)		
Acridine orange stain only	11/217 (5.1)	13/218 (6.0)
Gram's stain or acridine orange stain	12/217 (5.5)	16/218 (7.3)

* There were no significant differences in the baseline characteristics between the study groups. CSF denotes cerebrospinal fluid.

† Scores on the Glasgow Coma Scale range from 3 (deep coma) to 15 (normal neurologic status).

‡ In the dexamethasone group, one patient had cryptococcal meningitis and four had tuberculous meningitis. In the placebo group, five patients had tuberculous meningitis and two had parasitic eosinophilic meningitis.

§ In the dexamethasone group, three patients were infected with *S. intermedius*, one with *S. bovis*, and two with non-Lancefield grouping α -hemolytic streptococci. In the placebo group, one patient was infected with *S. intermedius*, two with *S. bovis*, seven with non-Lancefield grouping, optochin-resistant, α -hemolytic streptococci, and two with *S. agalactiae*.

¶ In the dexamethasone group, one patient was infected with *Pseudomonas aeruginosa*, and one with bacteroides species. In the placebo group, one patient was infected with *Proteus mirabilis*, and one with bacteroides species.

|| In the dexamethasone group, nine patients were infected with gram-positive cocci and three with gram-negative bacilli. In the placebo group, 11 patients were infected with gram-positive cocci and 5 with gram-negative bacilli.

in the cerebrospinal fluid. Two patients in the dexamethasone group and four in the placebo group were lost to follow-up 1 month after randomization (Fig. 1).

The baseline clinical characteristics of the patients were similar in the two study groups (Table 1). *S. suis* caused the highest proportion

of cases (a total of 116, of which 115 were serotype 2), followed by *S. pneumoniae* (55 cases). Of the 3 patients with *Staphylococcus aureus* meningitis (2 receiving dexamethasone, and 1 placebo), 2 patients also received oxacillin and 1 patient (with a methicillin-resistant isolate) received vancomycin. Forty patients (19 receiving dexamethasone,

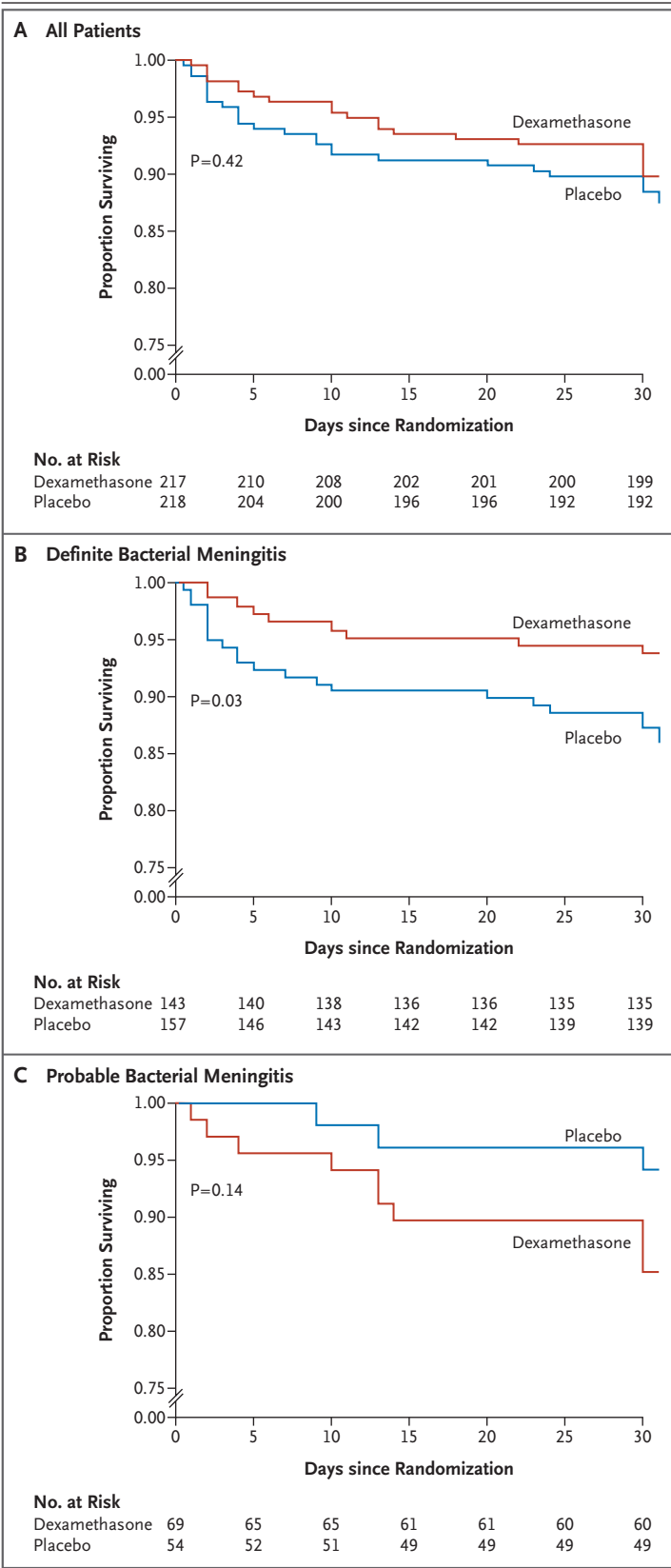


Figure 2. Kaplan–Meier Survival Estimates According to Study Group.

Panel A shows survival estimates for all patients who underwent randomization (intention-to-treat analysis). Panel B shows survival estimates for patients with definite bacterial meningitis, and Panel C estimates for patients with probable bacterial meningitis. P values are based on the log-rank test.

and 21 placebo) were treated with a combination of ceftriaxone and vancomycin, and 26 patients (11 receiving dexamethasone, and 15 placebo) with a combination of ceftriaxone and rifampin. Of 55 *S. pneumoniae* isolates, 50 (90.9%) were susceptible to ceftriaxone (minimal inhibitory concentration [MIC], $\leq 0.5 \mu\text{g}$ per milliliter) and 5 (9.1%) had intermediate resistance to ceftriaxone (MIC, >0.5 to $1.0 \mu\text{g}$ per milliliter). The rest of the bacterial isolates, with the exception of *Pseudomonas aeruginosa* (in 1 patient), *S. aureus* (in 1), and *Escherichia coli* (in 1), were susceptible to ceftriaxone.

All but four patients were tested for HIV infection; only three were infected (Table 1). One of these three had tuberculous meningitis, one had cryptococcal meningitis, and one had *S. pneumoniae* meningitis (the first two received dexamethasone, and the third placebo).

INTENTION-TO-TREAT ANALYSIS OF PRIMARY OUTCOME

Thirty days after randomization, 22 of the 217 patients in the dexamethasone group (10.1%) and 27 of the 218 patients in the placebo group (12.4%) had died (relative risk of death in the dexamethasone group, 0.79; 95% confidence interval [CI], 0.45 to 1.39) (Fig. 2A). The study drug was withdrawn early in 10 patients in each group, in most cases because a diagnosis other than bacterial meningitis was made. Among these patients, all but one (who had received dexamethasone) survived. The results of per-protocol analyses were similar to the results of intention-to-treat analyses for all primary and secondary outcomes.

PRESPECIFIED SUBGROUP ANALYSIS

The primary outcome was compared among subgroups of patients defined according to the diagnosis (definite bacterial meningitis, probable bacterial meningitis, or a different diagnosis) (Table 2). There was significant heterogeneity of the treatment effect across these diagnostic groups, but

Table 2. Prespecified Subgroup Analysis of the Relative Risk of Death at 1 Month.

Subgroup	No. of Patients	No. of Deaths*	Relative Risk of Death in the Dexamethasone Group (95% CI)	P Value	P Value for Heterogeneity Test†	Pooled Relative Risk of Death in the Dexamethasone Group (95% CI)‡	P Value
Definite bacterial meningitis	300	29	0.43 (0.20–0.94)	0.033	0.02§		
Probable bacterial meningitis	123	13	2.65 (0.73–9.63)	0.139			
Alternative diagnosis	12	5	1.67 (0.28–10.02)	0.228			
Previous antibiotics	261	29	0.68 (0.33–1.31)	0.302	0.84	0.66 (0.35–1.22)	0.18
No previous antibiotics	140	11	0.66 (0.35–1.97)	0.393			
Male sex	316	29	0.53 (0.25–1.13)	0.101	0.053	0.78 (0.44–1.36)	0.38
Female sex	117	18	1.38 (0.54–3.51)	0.495			
Age ≤50 yr	291	22	0.71 (0.31–1.65)	0.628	0.94	0.69 (0.38–1.27)	0.29
Age >50 yr	130	20	0.67 (0.29–1.59)	0.409			
<i>Streptococcus pneumoniae</i>	55	5	—¶	0.028	0.01		
Other cause	368	37	0.92 (0.49–1.73)	0.797			
<i>S. suis</i>	116	3	—¶	0.070	0.052	0.75 (0.41–1.36)	0.35
Other cause	307	39	0.86 (0.46–1.58)	0.624			
Gram-positive bacteria	218	17	0.06 (0.01–0.45)	0.006	<0.001		
Gram-negative bacteria	56	11	1.65 (0.52–5.21)	0.391			
Bacteria not seen or cultured	149	19	3.16 (0.88–11.31)	0.078			

* There were no deaths in the placebo group.

† The heterogeneity was calculated by fitting the Cox regression model with interaction terms. In case of zero events in one of the groups, the relative risk was set to a very small or a very large number (when the relative risk was equal to 0 or infinity), so the test lacks accuracy.

‡ Results were obtained from the stratified Cox regression model.

§ P=0.01 for heterogeneity of the treatment effect between the group with definite bacterial meningitis and the group with probable bacterial meningitis.

¶ There were no deaths in the dexamethasone group.

|| The P value is based on a log-rank test.

dexamethasone significantly improved survival in the group of patients with definite bacterial meningitis (relative risk of death, 0.43; 95% CI, 0.20 to 0.94) (Fig. 2B). Strata-specific analysis suggested that dexamethasone may even have been harmful in patients with probable bacterial meningitis, although the results were not significant (Fig. 2C).

The treatment effect in patients with definite bacterial meningitis was examined by comparing subgroups defined by the bacterial species isolated. This analysis suggested that the effect of dexamethasone was greatest in patients with meningitis caused by gram-positive cocci. Comparison of patients with meningitis caused by either *S. suis* or *S. pneumoniae* suggested a significant association between dexamethasone treatment and improved survival among patients with meningitis caused by *S. pneumoniae* (P=0.03).

EXPLORATORY SUBGROUP ANALYSIS

The effect of dexamethasone on survival 1 month after randomization in patients with definite or

probable meningitis was examined in subgroups defined by the Glasgow Coma Scale score on admission (15 or <15). There was no evidence of heterogeneity of the treatment effect between the subgroups. Among patients with a Glasgow Coma Scale score of 15 (147 patients), the relative risk of death was 4.16 (95% CI, 0.32 to 29.40); among patients with a score of less than 15 (276 patients), the relative risk of death was 0.63 (95% CI, 0.33 to 1.19).

We also examined whether antibiotic treatment before randomization influenced the treatment effect. Information regarding prior antibiotic use was available for 401 patients: 261 had received antibiotics and 140 had not. There was no evidence of heterogeneity of the treatment effect between the groups (P=0.84), and the stratified relative risk of death was 0.66 (95% CI, 0.35 to 1.22).

SECONDARY-OUTCOME ANALYSIS

Table 3 presents the proportions of patients who had died, were disabled, or were fully recovered

Table 3. Rates of Death and Disability 6 Months after Randomization.

Outcome	Dexamethasone	Placebo	P Value	
			Chi-Square Test	Chi-Square Test for Trend
All patients			0.627	0.458
No. of patients	217	218		
Death — no. (%)	22 (10.1)	26 (11.9)		
Severe disability — no. (%)	22 (10.1)	29 (13.3)		
Mild sequelae — no. (%)	57 (26.3)	54 (24.8)		
Full recovery — no. (%)	114 (52.5)	105 (48.2)		
Loss to follow-up — no. (%)	2 (0.9)	4 (1.8)		
Definite bacterial meningitis			0.199	0.080
No. of patients	143	157		
Death — no. (%)	9 (6.3)	22 (14.0)		
Severe disability — no. (%)	16 (11.2)	21 (13.4)		
Mild sequelae — no. (%)	45 (31.5)	45 (28.7)		
Full recovery — no. (%)	69 (48.3)	73 (46.5)		
Loss to follow-up — no. (%)	0	0		
Probable bacterial meningitis			0.153	0.376
No. of patients — no. (%)	69	54		
Death — no. (%)	10 (14.5)	2 (3.7)		
Severe disability — no. (%)	5 (7.2)	8 (14.8)		
Mild sequelae — no. (%)	12 (17.4)	9 (16.7)		
Full recovery — no. (%)	40 (58.0)	32 (59.3)		
Loss to follow-up — no. (%)	2 (2.9)	3 (5.6)		

at 6 months. On the basis of the intention-to-treat analysis, the proportion of patients who had died or were severely disabled was smaller in the dexamethasone group (44 of 217, or 20.3%) than in the placebo group (55 of 218, or 25.2%) (odds ratio in the dexamethasone group, 0.75; 95% CI, 0.48 to 1.18). Among the patients with definite bacterial meningitis, 43 of 157 (27.4%) in the placebo group had died or were severely disabled at 6 months, as compared with 25 of 143 (17.5%) in the dexamethasone group (odds ratio, 0.56; 95% CI, 0.32 to 0.98). A beneficial effect was not observed in the group of patients with probable bacterial meningitis who received dexamethasone (odds ratio for severe disability or death, 1.22; 95% CI, 0.54 to 2.99). Among patients with either definite or probable bacterial meningitis who were given dexamethasone, 40 of 212 (18.9%) died or were severely disabled as

compared with 53 of 211 (25.1%) who were given placebo (odds ratio, 0.69; 95% CI, 0.44 to 1.10).

Audiometry was performed in 180 of 195 patients (92.3%) in the dexamethasone group and in 177 of 191 (90.8%) in the placebo group. On the basis of the intention-to-treat analysis, 14 of the 180 patients in the dexamethasone group (7.8%) were deaf in one ear, and 7 of 180 (3.9%) were deaf in both ears, as compared with 21 of 177 (11.9%) and 16 of 177 (9.0%), respectively, in the placebo group ($P=0.047$). In subgroup analyses, dexamethasone was associated with a significant reduction in the proportion of patients with deafness in at least one ear. Among patients with definite meningitis, 12 of 125 (9.6%) in the dexamethasone group had deafness, as compared with 28 of 129 (21.8%) in the placebo group ($P=0.008$); among patients with definite or probable meningitis, 21 of 179 (11.7%) in the dexa-

methasone group had deafness, as compared with 37 of 174 (21.3%) in the placebo group ($P=0.02$). In the group of patients with *S. suis* meningitis, 20 of 53 (37.7%) given placebo were deaf in at least one ear, as compared with 7 of 57 (12.3%) given dexamethasone ($P=0.003$).

ADVERSE EVENTS

The study drug was withdrawn in one patient in each study group after 3 days because of bleeding in the upper gastrointestinal tract. Other, minor gastrointestinal bleeding was observed in 10 of the 217 patients (4.6%) given dexamethasone and 5 of the 218 patients (2.3%) given placebo ($P=0.20$); none of the patients with blood loss required transfusions, and there was no difference in the incidence of other common corticosteroid-associated adverse events, including clinically significant hyperglycemia and hypertension. Herpes labialis was a common complication but was not associated with dexamethasone treatment, occurring in 33 patients (15.2%) in the dexamethasone group and 30 (13.8%) in the placebo group ($P=0.69$). No life-threatening adverse events were reported in either study group.

MULTIVARIATE ANALYSIS

Among patients with definite bacterial meningitis, death at 1 month was associated with assignment to the placebo group (relative risk, 4.79; 95% CI, 1.78 to 12.91) and with older age (relative risk, 1.04; 95% CI, 1.02 to 1.07), lower Glasgow Coma Scale score (relative risk, 1.19; 95% CI, 1.04 to 1.36), the presence of hemiparesis (relative risk, 3.87; 95% CI, 1.39 to 10.7), and meningitis caused by a bacterium other than *S. suis* (relative risk, 6.94; 95% CI, 1.04 to 23.70). The variables associated with death at 1 month among patients with definite or probable disease are shown in Table 4. The combined variable of probable bacterial meningitis treated with dexamethasone was added to the model because of the observed heterogeneity of the treatment effect across these groups. The final model showed a significant interaction ($P=0.005$ by the likelihood-ratio test).

DISCUSSION

The results of this study show that treatment with adjunctive dexamethasone did not signifi-

Table 4. Relative Risk of Death for the Independent Predictors among Patients with Definite or Probable Meningitis.

Variable	Relative Risk of Death (95% CI)*	P Value
Age (per year)	1.03 (1.02–1.05)	0.001
Hemiparesis (yes or no)	3.40 (1.54–7.49)	0.002
Glasgow Coma Scale score (per unit increase)†	0.84 (0.76–0.93)	0.002
<i>Streptococcus suis</i> meningitis (yes or no)	0.16 (0.05–0.53)	0.003
Duration of symptoms (per day)	1.10 (1.04–1.15)	0.001
Definite bacterial meningitis (yes or no)		
Treated with placebo	1.00	
Treated with dexamethasone	0.22 (0.08–0.58)	0.002
Probable bacterial meningitis (yes or no)		
Treated with placebo	0.15 (0.04–0.58)	0.006
Treated with dexamethasone	0.38 (0.15–0.96)	0.04

* Relative risk was calculated per unit increase for the continuous variables; for hemiparesis the reference group was “no hemiparesis”; for *Streptococcus suis* meningitis the reference group was “no *S. suis* meningitis”; and for treatment categories the reference group was “definite bacterial meningitis treated with placebo.”

† Scores on the Glasgow Coma Scale range from 3 (deep coma) to 15 (normal neurologic status).

cantly improve survival in all adolescents and adults with suspected bacterial meningitis. An a priori subgroup analysis revealed significant heterogeneity of the treatment effect and suggested that dexamethasone significantly increased survival, and reduced disability and deafness, among patients with definite bacterial meningitis.

The lack of a treatment effect in patients with probable bacterial meningitis is a challenging finding. Evidence from animal models suggests that adjunctive corticosteroid therapy is most beneficial early in the disease, and administration is typically recommended only before the first dose of antibiotics.⁴ In our trial, 61.3% of the patients enrolled had prior antibiotic treatment, which may explain why microbiologic proof was not possible in 28.2% and why a treatment effect was not seen in this group. However, an exploratory subanalysis suggested that prior antibiotic use alone did not influence the treatment effect. More worrisome was the finding, in the multivariate analysis, that treatment of probable bacterial meningitis with dexamethasone was an independent risk factor for death at 1 month. We suspect that the reason for this finding is that a small proportion of the patients with a diagno-

sis of probable bacterial meningitis actually had tuberculous meningitis. Tuberculous meningitis is the most common cause of bacterial meningitis in our hospital and is difficult to diagnose. Indeed, 11 patients (8 in the dexamethasone group and 3 in the placebo group) were subsequently treated for tuberculous meningitis on clinical grounds; 6 of these patients died (all had received dexamethasone). In view of the fact that these deaths constitute half of all the deaths in the group with probable bacterial meningitis, they may have had an important influence on the results. The administration of dexamethasone without antituberculosis drugs is hazardous, and delayed therapy is an independent risk factor for death from tuberculous meningitis.⁹

Dexamethasone was associated with reduced deafness in all patients enrolled in the study, although the effect was particularly marked in those with *S. suis* meningitis. This is an important finding for physicians in Asia, where *S. suis* is a common cause of bacterial meningitis and leads to deafness in approximately 50% of patients.^{10,11} Indeed, the high proportion of *S. suis* meningitis in this trial may affect the extent to which the results can be generalized. We believe it is unlikely that dexamethasone affects the outcome of *S. suis* meningitis but not that of meningitis caused by other pyogenic bacteria. The presenting clinical features and the cerebrospinal fluid white-cell count and total protein and glucose con-

centrations are similar in patients with *S. suis* meningitis and those with meningitis from other common bacterial causes.^{11,12} The immunosuppressive effects of dexamethasone are broad and are unlikely to influence the outcome by targeting pathogen-specific differences in pathophysiology, although the mechanisms by which dexamethasone improves the outcome are unclear. A post hoc analysis of data from the European trial of dexamethasone in patients with bacterial meningitis suggested that dexamethasone reduced the systemic rather than the neurologic complications of pneumococcal meningitis.^{7,13} The systemic complications of *S. suis* infection are similar to those of *S. pneumoniae* infection: bacteremia, sepsis, and a purpuric rash occur in similar proportions of patients with the two types of infection.¹¹

In summary, dexamethasone does not improve the outcome in all adolescents and adults with suspected bacterial meningitis. However, a significant beneficial effect is seen in patients with microbiologically proven disease, including those who have received prior treatment with antibiotic therapy.

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