Dexamethasone for the Treatment of Tuberculous Meningitis in Adolescents and Adults

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ABSTRACT

BACKGROUND

Tuberculous meningitis kills or disables more than half of those affected with the disease. Previous studies have been too small to determine whether adjunctive treatment with corticosteroids can reduce the risk of disability or death among adults with tuberculous meningitis, and the effect of coinfection with the human immunodeficiency virus (HIV) is unclear.

METHODS

We performed a randomized, double-blind, placebo-controlled trial in Vietnam in patients over 14 years of age who had tuberculous meningitis, with or without HIV infection, to determine whether adjunctive treatment with dexamethasone reduced the risk of death or severe disability after nine months of follow-up. We conducted prespecified subgroup analyses and intention-to-treat analyses.

RESULTS

A total of 545 patients were randomly assigned to groups that received either dexamethasone (274 patients) or placebo (271 patients). Only 10 patients (1.8 percent) had been lost to follow-up at nine months of treatment. Treatment with dexamethasone was associated with a reduced risk of death (relative risk, 0.69; 95 percent confidence interval, 0.52 to 0.92; P=0.01). It was not associated with a significant reduction in the proportion of severely disabled patients (34 of 187 patients [18.2 percent] among survivors in the dexamethasone group vs. 22 of 159 patients [13.8 percent] in the placebo group, P=0.27) or in the proportion of patients who had either died or were severely disabled after nine months (odds ratio, 0.81; 95 percent confidence interval, 0.58 to 1.13; P=0.22). The treatment effect was consistent across subgroups that were defined by disease-severity grade (stratified relative risk of death, 0.68; 95 percent confidence interval, 0.52 to 0.91; P=0.007) and by HIV status (stratified relative risk of death, 0.78; 95 percent confidence interval, 0.59 to 1.04; P=0.08). Significantly fewer serious adverse events occurred in the dexamethasone group than in the placebo group (26 of 274 patients vs. 45 of 271 patients, P=0.02).

CONCLUSIONS

Adjunctive treatment with dexamethasone improves survival in patients over 14 years of age with tuberculous meningitis but probably does not prevent severe disability.

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Tuberculous meningitis is the severest form of infection with *Mycobacterium tuberculosis,* causing death or severe neurologic deficits in more than half of those affected in spite of antituberculosis chemotherapy.[1,2] Attenuation of the inflammatory response in bacterial and mycobacterial meningitis may improve outcome by reducing the likelihood or severity of neurologic complications. Early studies suggested that corticosteroids reduced cerebrospinal fluid inflammation and time to recovery in patients with tuberculous meningitis, but the studies were too small to confirm any effect on survival.[3-7] Concern remained that corticosteroids might reduce the case fatality rate but increase the number of disabled patients.[8] Randomized trials performed in Egypt[9] and South Africa[10] provided evidence that corticosteroids improved survival in children with severe disease and probably reduced neurologic sequelae.

A meta-analysis of all randomized controlled trials of corticosteroids for tuberculous meningitis suggested that corticosteroids were effective in reducing the risk of death in children (relative risk, 0.77; 95 percent confidence interval, 0.62 to 0.96) but not in patients over 14 years of age (relative risk, 0.96; 95 percent confidence interval, 0.50 to 1.84), although only six trials involving a total of 595 patients (158 adults) met the inclusion criteria,[11] and there were no data on patients coinfected with the human immunodeficiency virus (HIV). The authors concluded that small numbers of patients, poor concealment of the treatment-group assignments, and publication bias could account for the positive results, and that studies in patients with HIV infection and studies of a size large enough to assess morbidity and the case fatality rate were required.[11] Therefore, we conducted a double-blind, placebo-controlled trial to determine whether adjunctive dexamethasone therapy improves the outcome in patients over 14 years of age who have tuberculous meningitis, with or without HIV infection.

METHODS

STUDY PARTICIPANTS

We recruited study participants from two centers in Ho Chi Minh City, Vietnam: Pham Ngoc Thach Hospital for Tuberculosis and Lung Disease and the Hospital for Tropical Diseases. These 500-bed hospitals serve the local community and act as tertiary referral centers for patients with severe tuberculosis (Pham Ngoc Thach Hospital) or infectious diseases (Hospital for Tropical Diseases) in southern Vietnam.

Only patients over 14 years of age with clinical evidence of meningitis (defined as the combination of nuchal rigidity and cerebrospinal fluid abnormalities) were eligible to enter the study. Tuberculous meningitis was defined as "definite" if acid-fast bacilli were seen in the cerebrospinal fluid. It was defined as "probable" in patients with one or more of the following: suspected active pulmonary tuberculosis on chest radiography, acid-fast bacilli found in any specimen other than the cerebrospinal fluid, and clinical evidence of other extrapulmonary tuberculosis. Tuberculous meningitis was defined as "possible" in patients with at least four of the following: a history of tuberculosis, predominance of lymphocytes in the cerebrospinal fluid, a duration of illness of more than five days, a ratio of cerebrospinal fluid glucose to plasma glucose of less than 0.5, altered consciousness, yellow cerebrospinal fluid, or focal neurologic signs.

Patients were reclassified on discharge as having definite tuberculous meningitis if acid-fast bacilli were seen or *M. tuberculosis* was cultured from the cerebrospinal fluid, or as not having tuberculous meningitis if another diagnosis was confirmed by microbiologic or histopathological evaluation.

Patients were not eligible to enter the trial if the enrolling physician believed that corticosteroids were contraindicated, if the patient had received more than one dose of any corticosteroid or more than 30 days of antituberculosis chemotherapy immediately before study entry, or if the consent of either the patient or the patient's relatives was not obtained.

The ethics and scientific committees of both hospitals, the Health Services of Ho Chi Minh City, and the Oxfordshire Clinical Research Ethics Committee approved the study protocol. The funding body played no part in the design, implementation, or analysis of the study or in the decision to publish the results. Written informed consent to participate in the study was obtained from all patients or from their relatives if the patient could not provide consent.

LABORATORY INVESTIGATIONS

Cerebrospinal fluid specimens were stained and cultured by standard methods for pyogenic bacteria, fungi, and mycobacteria. Isolates of *M. tuberculosis* were tested for susceptibility to isoniazid,

rifampin, pyrazinamide, ethambutol, and streptomycin.

All patients were tested for antibodies to HIV and hepatitis B surface antigen. CD4 lymphocyte counts were performed by flow cytometry (FACSCalibur, Becton Dickinson) for all HIV-infected adults as soon as possible after randomization.

TREATMENT

Adults previously untreated for tuberculosis received three months of daily oral isoniazid (5 mg per kilogram of body weight), rifampin (10 mg per kilogram), pyrazinamide (25 mg per kilogram; maximum, 2 g per day), and intramuscular streptomycin (20 mg per kilogram; maximum, 1 g per day), followed by six months of isoniazid, rifampin, and pyrazinamide at the same daily doses. Ethambutol (20 mg per kilogram; maximum, 1.2 g per day) was substituted for streptomycin in the cases of HIV-infected patients and was added to the regimen for three months for patients who had been treated previously for tuberculosis. Drugs were administered by nasogastric tube to patients who were unable to swallow. None of the patients received antiretroviral drugs.

Patients were stratified on entry according to the British Medical Research Council criteria, modified as follows[12]: patients with grade I disease had a score on the Glasgow Coma Scale of 15 (possible range, 3 to 15, with higher scores indicating better status) with no focal neurologic signs; patients with grade II had a score of either 11 to 14, or of 15 with focal neurologic signs; and patients with grade III had a score of 10 or less. Patients within each grade were randomly assigned to receive dexamethasone sodium phosphate or placebo (VIDIPHA, Vietnam) as soon as possible after the start of antituberculosis treatment. Patients with grade II or III disease received intravenous treatment for four weeks (0.4 mg per kilogram per day for week 1, 0.3 mg per kilogram per day for week 2, 0.2 mg per kilogram per day for week 3, and 0.1 mg per kilogram per day for week 4) and then oral treatment for four weeks, starting at a total of 4 mg per day and decreasing by 1 mg each week.

Prolonged intravenous dexamethasone treatment of patients with mild disease was not considered acceptable. Therefore, patients with grade I disease received two weeks of intravenous therapy (0.3 mg per kilogram per day for week 1 and 0.2 mg per kilogram per day for week 2) and then four weeks of oral therapy (0.1 mg per kilogram per day for week 3, then a total of 3 mg per day, decreasing by 1 mg each week). The concentration of dexamethasone, and the absence of dexamethasone from placebo, were confirmed by liquid chromatography and mass spectroscopy performed on 10 randomly selected vials of the study drug and placebo.

A computer-generated sequence of random numbers was used to allocate treatment in blocks of 30. Numbered individual treatment packs containing the study drug were prepared for the duration of treatment and were distributed for sequential use once a patient fulfilled the entry criteria. Parenteral placebo and dexamethasone were identical in appearance, as were oral placebo and dexamethasone.

The attending physicians were responsible for enrolling the participants and ensuring that the study drug was given from the correct treatment pack. Daily monitoring of all inpatients by one of the authors ensured uniform management between sites and accurate recording of clinical data in individual study notes. All participants, enrolling physicians, and investigators remained blinded to the treatment allocation until the last patient completed follow-up.

ASSESSMENT OF OUTCOME

The primary outcome was death or severe disability nine months after randomization. Two experienced Vietnamese physicians at each site were trained to assess disability with the Rankin scale and the "simple questions" score, two well-validated measures of outcome from stroke that have good interobserver agreement.[13,14] The simple questions categorized outcome in survivors by determining whether they required help with everyday activities such as eating, washing, and going to the toilet. If the patients answered yes, they were regarded as severely disabled. If they answered no, they were asked whether the illness had left them with any other problems. If so, the outcome was designated "intermediate"; if not, the outcome was "good."

The Rankin scale also assessed dependence. A score of 0 indicated no symptoms; 1 indicated minor symptoms not interfering with lifestyle; 2 indicated symptoms that might restrict lifestyle, but patients could look after themselves; 3 indicated symptoms that restricted lifestyle and prevented independent living; 4 indicated symptoms that prevented independent living, although constant care and attention were not required; and 5 indicated to-

tal dependence on others, requiring help day and night. The classification of outcomes as "good" (a score of 0), "intermediate" (scores of 1 or 2), or "severe disability" (scores of 3, 4, or 5) was defined before the start of the trial. Patients were assessed at one, two, six, and nine months after randomization, and at each point the worst score from either questionnaire was taken as the outcome.

Secondary outcome measures were coma-clearance time (days from randomization until observation of a Glasgow coma score of 15 for more than two consecutive days), fever-clearance time (days from randomization until observation of a maximal daily temperature of less than 37.5°C for more than five consecutive days), time to discharge from the hospital, time to relapse (defined by the onset of new focal neurologic signs or a fall in the Glasgow coma score of 2 points or more for two or more days after more than seven days of clinical stability or improvement at any time after randomization), and the presence of focal neurologic deficit nine months after randomization. These outcome measures were assessed daily by means of clinical examination by the principal investigator or by the physicians trained to assess disability. All data were recorded prospectively into individual study notes, entered into an electronic database (Microsoft FoxPro, Version 6.0), and double-checked before analysis.

STATISTICAL ANALYSIS

The case fatality rate for tuberculous meningitis in adult patients in the two hospitals before the study (when corticosteroids were not routinely administered) was 35 percent. We calculated that 270 patients would be required in each group to provide at least 80 percent power to detect a 31 percent reduction in the case fatality rate, from 35 percent to 24 percent, with a two-sided significance level of 5 percent.

The outcomes were evaluated by intention-to-treat analyses and prespecified subgroup analyses. We used Kaplan–Meier estimates to display the survival experiences of the two treatment groups and the log-rank test to evaluate the equality of the survival distributions. 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 Cox regression. The combined outcome of death or severe disability by nine months was compared between the groups by the chi-square test, and the

odds ratio for the outcome was calculated with the use of logistic regression. The last recorded disability score was considered to be the score at nine months for patients who did not complete follow-up. The prespecified subgroup analysis compared the primary outcome among subgroups of patients defined according to HIV-infection status, the British Medical Research Council grade, and diagnostic group (definite, probable, or possible tuberculous meningitis). Tests of interaction between subgroups and the assigned treatment were performed by a Cox regression model for survival data and by logistic-regression analysis (with the use of the likelihood-ratio test) for the combined outcome data.

The times to fever clearance, coma clearance, relapse, and discharge were summarized in each treatment group with the use of Kaplan–Meier estimates and were compared with the use of the log-rank test. The proportion of patients with focal neurologic deficit by nine months and the frequency of adverse events were compared with the use of the chi-square test. Multivariable analysis of baseline variables identified independent risk factors for death. The analysis was performed with the use of SPSS and Stata software. All reported P values are two-sided.
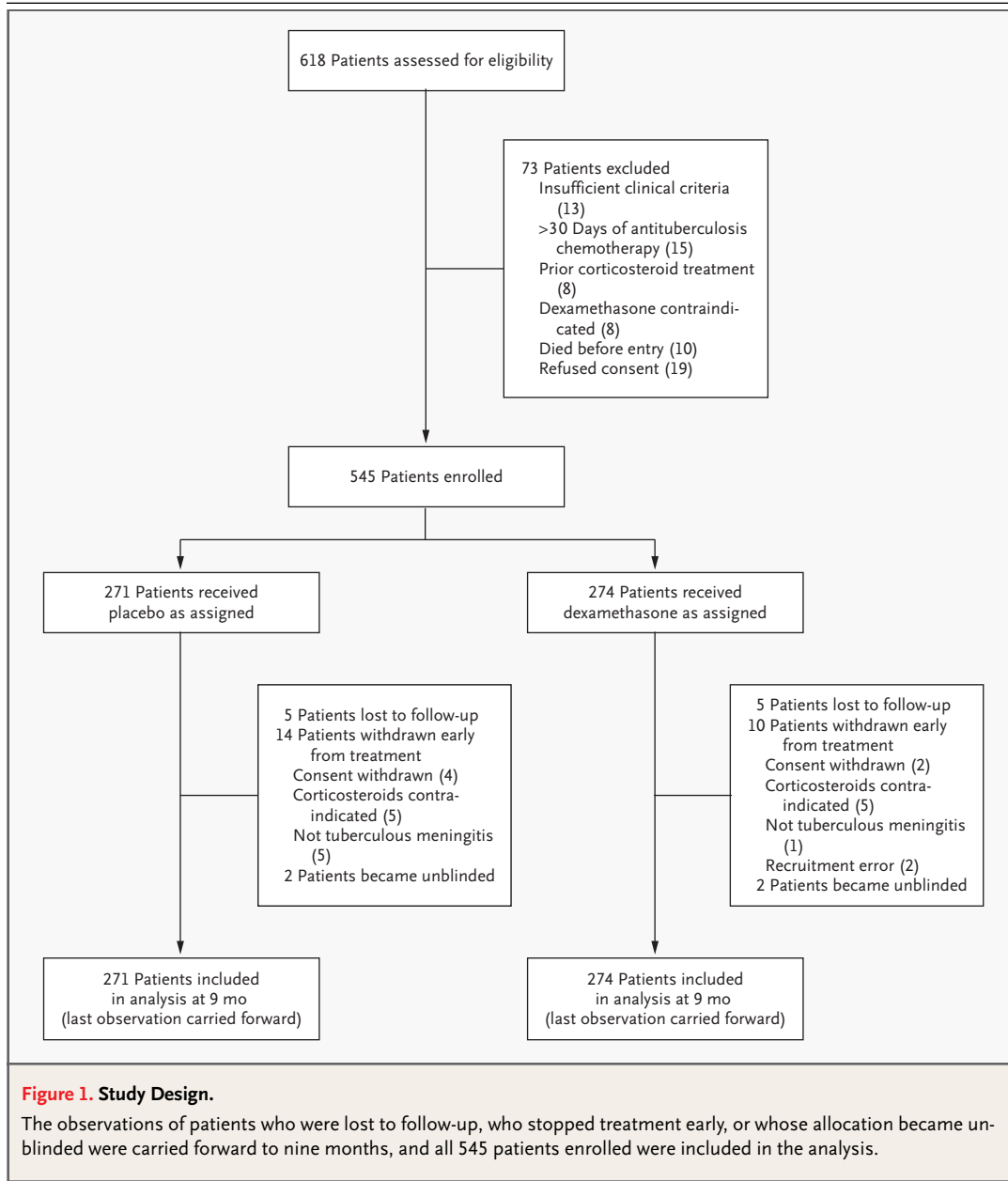
The independent data and safety monitoring committee reviewed the results of the study after 20 deaths, after one year of recruitment, and after the enrollment of 520 patients. The predefined criterion for stopping the trial early was a difference of more than 3 SD in the proportion who died in each group; the trial was not stopped early.

RESULTS

A total of 545 patients over 14 years of age were randomly assigned to receive either dexamethasone (274 patients) or placebo (271 patients) from April 4, 2001, to March 29, 2003 (Fig. 1). Median follow-up was 274 days (range, 28 to 442). Ten patients did not complete the nine-month follow-up (five in each group): five were lost to follow-up after one month (one in the dexamethasone group), three after two months (two in the dexamethasone group), and one after three months and one after four months (both in the dexamethasone group). Severe disability was recorded in 4 of the 10 patients (3 in the dexamethasone group), an intermediate outcome in 2 of 10 (1 in the dexamethasone group), and a good outcome in 4 of 10 (1 in the dexamethasone group).

Figure 1. Study Design.

The observations of patients who were lost to follow-up, who stopped treatment early, or whose allocation became unblinded were carried forward to nine months, and all 545 patients enrolled were included in the analysis.

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BASELINE CHARACTERISTICS OF THE PATIENTS

The baseline characteristics at randomization were similar in the dexamethasone and placebo groups (Table 1), although a higher proportion of the placebo group was infected with HIV (19.9 percent vs. 16.1 percent). *M. tuberculosis* was cultured from the cerebrospinal fluid or another site in 170 patients (31.2 percent), 85 from each group. Of 170 isolates, 99 (58.2 percent) were susceptible to all first-line drugs (51 in the placebo group and 48 in the dexamethasone group), 60 (35.3 percent) were resistant to streptomycin, isoniazid, or both (29 in the placebo group and 31 in the dexamethasone group), 1 was monoresistant to rifampin (in the dexamethasone group), and 10 (5.9 percent) were resistant to at least isoniazid and rifampin (3 in the placebo

Table 1. Baseline Characteristics of the Study Population.		
Variable	Dexamethasone (N=274)	Placebo (N=271)
Age — yr		
Median	36.0	35.0
Range	15–88	15–84
Male sex — no. (%)	168 (61.3)	163 (60.1)
Diagnosis at discharge — no. (%)		
Definite	98 (35.8)	89 (32.8)
Probable	130 (47.4)	131 (48.3)
Possible	44 (16.1)	47 (17.3)
Not tuberculous meningitis*	2 (0.7)	4 (1.5)
Duration of symptoms — days†		
Median	15	15
Range	4–90	2–90
Weight — kg		
Median	45.0	45.0
Range	25–75	30–70
Score on Glasgow coma scale‡		
Median	14	14
Range	3–15	3–15
Cranial nerve palsy — no. (%)	82 (29.9)	74 (27.3)
Hemiparesis — no. (%)	48 (17.5)	37 (13.7)
Paraparesis — no. (%)	28 (10.2)	11 (4.1)
MRC grade — no. (%)§		
I	90 (32.8)	86 (31.7)
II	122 (44.5)	125 (46.1)
III	62 (22.6)	60 (22.1)
HIV status — no. (%)		
Positive	44 (16.1)	54 (19.9)
Negative	227 (82.8)	209 (77.1)
Not tested	3 (1.1)	8 (3.0)
Lymphocyte count — per mm³¶		
CD4 cells		
Median	64	66
Range	14–694	7–359
CD8 cells		
Median	606	386
Range	134–998	28–1001

* Alternative diagnoses were made only with histologic or microbiologic evidence.
† Data were missing for one patient in each group.
‡ Scores on the Glasgow Coma Scale range from 3 (worst) to 15 (best), with 13 or higher indicating only mild brain injury.
§ MRC denotes British Medical Research Council criteria. Grade I indicates a Glasgow coma score of 15 with no neurologic signs, grade II a score of 11 to 14 (or 15 with focal neurologic signs), and grade III a score of 10 or less.
¶ CD4 and CD8 cell counts were performed only for HIV-infected patients. The counts were not performed in 12 of 54 HIV-infected patients in the placebo group and 6 of 44 in the dexamethasone group.

group and 7 in the dexamethasone group). (See the Supplementary Appendix, available with the complete text of this article at www.nejm.org.)

ANALYSIS OF THE PRIMARY OUTCOME

The proportion of patients with the combined outcome of death or severe disability nine months after randomization did not differ significantly between the groups, although treatment with dexamethasone was strongly associated with improved survival (Table 2). There was no significant difference between the proportions of survivors in each treatment group with severe disability (P=0.27), with an intermediate outcome (P=0.96), or with a good outcome (P=0.44) (Table 3). Outcomes based on the two types of disability scores agreed in all but one survivor, who was defined as severely disabled according to the score based on the simple questions and as intermediate according to the Rankin score. (See the Supplementary Appendix.)

ANALYSIS OF SECONDARY OUTCOMES

The time to fever clearance was significantly shorter in the dexamethasone group than in the placebo group (median, 9 vs. 11 days; P=0.03), but there was no significant difference between the dexamethasone and placebo groups in the time to coma clearance (median, 9 vs. 11 days, respectively; P=0.23) or the time to hospital discharge (median, 44 vs. 54 days; P=0.57).

Relapse occurred in 89 patients (16.3 percent), 41 (15.0 percent) in the dexamethasone group and 48 (17.7 percent) in the placebo group (P=0.42), with no significant difference in the time to relapse between the groups (median, 41 days in the dexamethasone group vs. 38 days in the placebo group; P=0.12).

In patients who had hemiparesis or paraparesis at baseline, hemiparesis resolved by nine months in 36 of 48 patients (75.0 percent) who were given dexamethasone and in 30 of 37 patients (81.1 percent) given placebo (P=0.51). Paraparesis resolved in 19 of 28 patients (67.9 percent) given dexamethasone and in 9 of 11 (81.8 percent) given placebo (P=0.46). In patients without hemiparesis at baseline, hemiparesis was present by nine months in 14 of 226 patients (6.2 percent) in the dexamethasone group and 11 of 234 patients (4.7 percent) in the placebo group (P=0.48). Paraparesis was present in 11 of 246 patients who did not have paraparesis at baseline (4.5 percent) in the dexamethasone group and 11 of 260 (4.2 percent) in the placebo group

Table 2. Outcome Nine Months after Randomization, According to Disease-Severity Grade and HIV Status.*

Outcome and Group	Dexamethasone	Placebo	Relative Risk (95% CI)	P Value
	no./total no. (%)			
Death				
All patients	87/274 (31.8)	112/271 (41.3)	0.69 (0.52–0.92)	0.01
Grade				
I	15/90 (16.7)	26/86 (30.2)	0.47 (0.25–0.90)	0.02
II	38/122 (31.1)	50/125 (40.0)	0.71 (0.46–1.1)	0.11
III	34/62 (54.8)	36/60 (60.0)	0.81 (0.51–1.29)	0.38
Relative risk of death stratified according to grade†			0.68 (0.52–0.91)	0.007
HIV status				
Negative	57/227 (25.1)	67/209 (32.1)	0.72 (0.51–1.02)	0.07
Positive	27/44 (61.4)	37/54 (68.5)	0.86 (0.52–1.41)	0.55
Undetermined	3/3 (100)	8/8 (100)	1.16 (0.71–1.91)	0.71
Relative risk of death stratified according to HIV status‡			0.78 (0.59–1.04)	0.08

	Dexamethasone	Placebo	Odds Ratio	P Value
	no./total no. (%)			
Death or severe disability				
All patients	121/274 (44.2)	134/271 (49.4)	0.81 (0.58–1.13)	0.22
Grade				
I	19/90 (21.1)	30/86 (34.9)	0.50 (0.25–0.98)	0.04
II	57/122 (46.7)	61/125 (48.8)	0.92 (0.56–1.52)	0.74
III	45/62 (72.6)	43/60 (71.7)	1.05 (0.47–2.31)	0.91
Odds ratio stratified according to grade§			0.79 (0.56–1.13)	0.20
HIV status				
Negative	93/230 (40.4)	96/217 (44.2)	0.86 (0.59–1.25)	0.42
Positive	28/44 (63.6)	38/54 (70.4)	0.74 (0.32–1.72)	0.48
Undetermined	3/3 (100)	8/8 (100)	—	—
Odds ratio stratified according to HIV status¶			0.87 (0.62–1.24)	0.44

* Grade I indicates a Glasgow coma score of 15 with no neurologic signs, grade II a score of 11 to 14 (or 15 with focal neurologic signs), and grade III a score of 10 or less. Scores on the Glasgow Coma Scale range from 3 (worst) to 15 (best). CI denotes confidence interval.
† For this test of heterogeneity, P=0.62.
‡ For this test of heterogeneity, P=0.55.
§ For this test of heterogeneity, P=0.27.
¶ For this test of heterogeneity, P=1.00.

(P=0.89). There were no significant differences between the groups in the proportions of survivors with clinically defined hearing loss or with reduced visual acuity.

PRESPECIFIED SUBGROUP ANALYSES

Dexamethasone treatment was not associated with a significant reduction in the combined outcome of death or severe disability nine months after randomization when we analyzed subgroups defined by disease-severity grade at baseline (Table 2). However, dexamethasone was associated with a significantly reduced risk of death after stratification according to the grade of disease.

The case fatality rate was higher among HIV-infected patients than among uninfected patients

Table 3. Outcomes of 545 Patients Nine Months after Randomization.

Group	No. of Patients	Outcome			
		Good	Inter-mediate	Severe Disability	Death
		number (percent)			
Dexamethasone*	274	104 (38.0)	49 (17.9)	34 (12.4)	87 (31.8)
Placebo	271	95 (35.1)	42 (15.5)	22 (8.1)	112 (41.3)

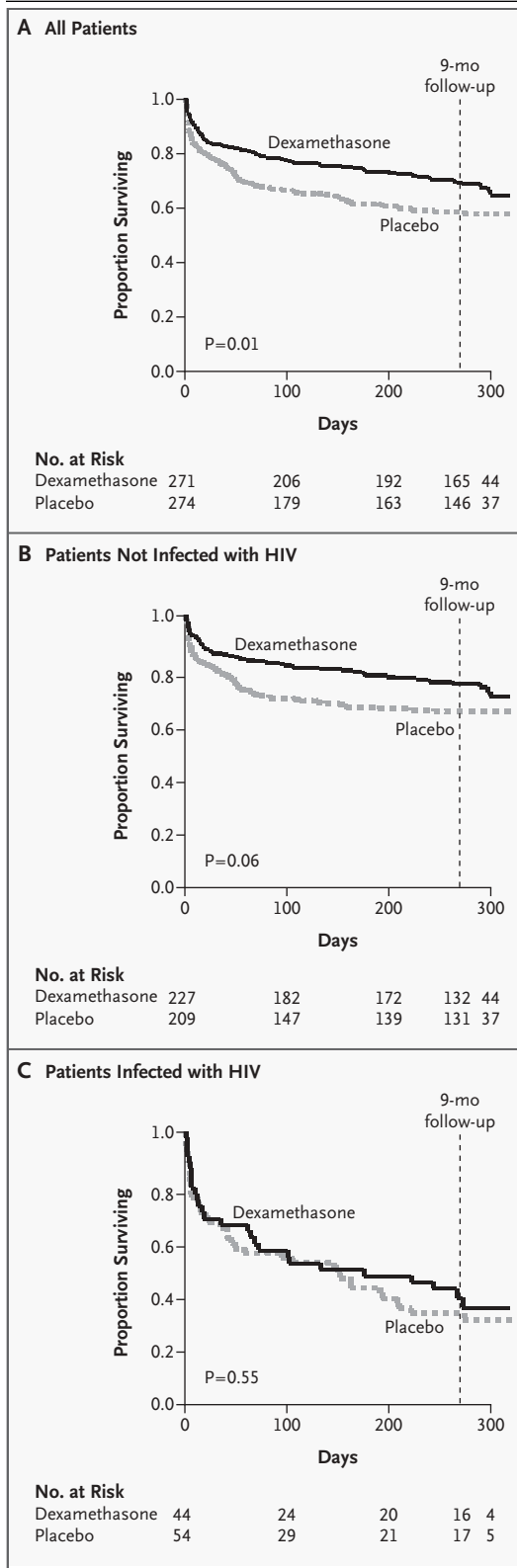* Because of rounding, the percentages for the dexamethasone group do not total 100.

(65.3 percent vs. 28.4 percent overall, P<0.001) regardless of treatment assignment. Although the number of HIV-infected patients was small, deaths in this group occurred at a constant rate throughout the 9 months of treatment, whereas deaths became infrequent after 50 days among patients not infected with HIV (Fig. 2). The effect of dexamethasone on the combined end point of death or disability and on death alone was homogeneous across the HIV subgroups, although the stratified subgroup analyses failed to confirm a significant association between dexamethasone and improvement in either outcome (Table 2).

The effect of dexamethasone treatment was homogeneous across the subgroups defined according to whether the patients had definite, probable, or possible tuberculous meningitis (tests of heterogeneity, P=0.11 for death or severe disability; P=0.53 for death) and was associated with a reduced risk of death (stratified relative risk, 0.68; 95 percent confidence interval, 0.52 to 0.91; P=0.007).

Multivariable analysis of baseline characteristics revealed that death was independently associated with a Glasgow coma score of 10 or less, hemiparesis, previous treatment for tuberculosis, the presence of extraneural or pulmonary tuberculosis, HIV infection, a low hematocrit, a low cerebro-

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

Panel A shows all 545 patients. Panel B shows the 436 patients who were not infected with HIV, and Panel C shows the 98 HIV-infected patients. The HIV status of 11 patients was not determined and was excluded from this analysis. P values were determined with the log-rank test.

A All Patients

No. at Risk
Dexamethasone 271   206   192   165 44
Placebo 274   179   163   146 37

B Patients Not Infected with HIV

No. at Risk
Dexamethasone 227   182   172   132 44
Placebo 209   147   139   131 37

C Patients Infected with HIV

No. at Risk
Dexamethasone 44   24   20   16 4
Placebo 54   29   21   17 5

spinal fluid leukocyte count, a low ratio of cerebrospinal fluid glucose to plasma glucose, an adverse event requiring alteration to the antituberculosis-drug dose or regimen, and treatment with placebo.

EXPLORATORY SUBGROUP ANALYSIS

Heterogeneity of treatment effect was examined among subgroups defined by age (≤18 years vs. >18 years) and by duration of symptoms at presentation (≤15 days vs. >15 days). Heterogeneity was found to be absent with respect to death (P=0.87 for age, P=0.61 for duration of symptoms) and death or severe disability (P=0.39 for age, P=0.49 for duration of symptoms). A significant reduction in the risk of death was observed after stratification according to age (relative risk, 0.69; 95 percent confidence interval, 0.52 to 0.93; P=0.01) and duration of symptoms (relative risk, 0.69; 95 percent confidence interval, 0.52 to 0.92; P=0.01).

ADVERSE EVENTS

Significantly more adverse events were reported in the placebo group than in the dexamethasone group (214 of 271 vs. 186 of 274, P=0.005); significantly more were severe in the placebo group than in the dexamethasone group (45 of 271 vs. 26 of 274, P=0.02) (Table 4). In particular, eight severe cases of hepatitis (one fatal) occurred in the placebo group, and none occurred in the dexamethasone group (P=0.004). The following adverse events led us to stop the study drug in 12 patients (5 in the dexamethasone group and 7 in the placebo group): gastrointestinal bleeding in 6 (3 in each group), bacterial sepsis in 4 (3 in the placebo group), and hypertension in 2 (1 in each group). The antituberculosis-drug dose or regimen was altered because of an adverse event on 62 occasions in the dexamethasone group and on 81 occasions in the placebo group, and changes in drug therapy were independently associated with death.

DISCUSSION

The results of this study show that adjunctive treatment with dexamethasone improved survival in patients over 14 years of age with tuberculous meningitis, but when the outcome measure was broadened to death or severe disability, there was no significant benefit. Meta-analysis of previous data is difficult, given variable methods of outcome assessment, loss to follow-up, and small numbers of survivors, but earlier studies suggested that corticosteroids reduced disability.[11] We assessed disability by means of two scores that have been well validated for the assessment of outcomes after stroke in the developed world[13] but not for other diseases in different settings. We sought to reduce intraobserver and interobserver variability by training four experienced Vietnamese physicians to assess all survivors, and there was excellent agreement in the scores they assigned. However, the scores may have lacked discriminative power in this setting, and we may have failed to detect a true effect. Data concerning focal neurologic sequelae suggest this failure is unlikely — dexamethasone did not affect the incidence or resolution of hemiparesis, paraparesis, or quadriparesis, which are the most common causes of severe disability due to tuberculous meningitis. Previous smaller studies have reported similar findings; the authors hypothesized that corticosteroids exert an effect by reducing basal meningeal inflammation and brain-stem encephalopathy but do not modify infarct-causing periarteritis.[10]

Dexamethasone may improve outcomes by reducing the frequency of adverse events that necessitate a change in the antituberculosis-drug dose or regimen (such change was an independent risk factor for death in our study) — severe clinical hepatitis, in particular. Studies of pulmonary tuberculosis showed that corticosteroids reduced the incidence of severe drug-hypersensitivity reactions,[15,16] but this effect has not been documented for other forms of tuberculosis and is not widely recognized. No increase in corticosteroid-related adverse events was observed in our study.

There are no previous data from controlled trials of corticosteroids for HIV-associated tuberculous meningitis. The 98 HIV-infected patients recruited to our trial were severely immunocompromised (median CD4 lymphocyte count, 66 per cubic millimeter), and none were treated with antiretroviral drugs. These patients had a higher case fatality rate than the patients who were not infected with HIV, and although it was not possible to determine the cause of death, undiagnosed opportunistic infections may have been a factor. The treatment effect of dexamethasone was homogeneous across HIV subsets, and stratified subgroup analysis showed that dexamethasone was associated with a reduction in the risk of death that was not significant (P=0.08). The numbers of HIV-infected patients were too small for us to confirm or reject confidently a treatment effect, and the results may not be generalizable to populations with access to antiret-

Table 4. Adverse Events According to Severity and Treatment Group.*						
Event	Dexamethasone (N=274)	Placebo (N=271)	P Value	Dexamethasone (N=274)	Placebo (N=271)	P Value
	no. with nonsevere event			*no. with severe event*		
Subclinical hepatitis†	42	50	0.39	0	0	
Clinical hepatitis‡	3	6	0.34	0	8	0.004
Gastrointestinal bleeding§	4	6	0.76	2	3	0.68
Bacterial sepsis¶	5	7		3	4	0.72
Septic shock	0	0		3	0	0.25
Brain herniation syndrome	0	0		1	4	0.21
Decrease in visual acuity	7	9	0.78	6	8	0.77
Hyponatremia (plasma sodium <130 mmol/liter)	4	7	0.53	1	6	0.07
Hyperglycemia (fasting plasma glucose >7.8 mmol/liter)	3	2	1.00	0	0	
Hypertension (>160/95 mm Hg for >2 days)	1	4	0.21	0	0	
Vertigo	18	21	0.71	0	0	
Deafness (on clinical examination)	4	4	1.00	3	3	1.00
Cushing's features	10	2	0.04	0	0	
Pruritus	4	8	0.37	0	0	
Polyarthralgia	1	4	0.21	0	0	
Streptomycin reaction‖	1	3	0.37	0	0	
Rifampin flu**	3	4	0.72	0	0	
Rash	9	4	0.27	1	0	1.00
Other††	44	32	0.19	6	9	0.59
Total	160	169	0.39	26	45	0.02

* A severe event was defined as any event causing or threatening to cause prolonged hospital stay, disability, or death.
† Subclinical hepatitis was defined as an increase in the aspartate aminotransferase or alanine aminotransferase level to more than twice the upper limit of normal that was not accompanied by clinical signs of hepatitis (e.g., jaundice, liver enlargement or tenderness, or vomiting).
‡ Clinical hepatitis was defined as an increase in the aspartate aminotransferase or alanine aminotransferase level to more than twice the upper limit of normal that was accompanied by clinical signs of hepatitis (e.g., jaundice, liver enlargement or tenderness, or vomiting).
§ Gastrointestinal bleeding was defined as oral or rectal gastrointestinal bleeding on visual inspection.
¶ Bacterial sepsis was confirmed microbiologically in blood or another sterile site of secondary pyogenic bacterial infection.
‖ Streptomycin reaction was defined as local or systemic reaction to the intramuscular injection of streptomycin.
** Rifampin flu was defined as persistent fever and influenza-like symptoms temporally related to the ingestion of rifampin (the symptoms stopped when the drug was stopped and recurred when the drug was restarted) with the exclusion of other possible infective diagnoses.
†† "Other" denotes events that were reported fewer than four times.

roviral drugs. These data suggest, however, that dexamethasone is safe and may be of benefit in this group of patients. Future studies should include patients who are taking antiretroviral drugs, and such patients should be monitored carefully for opportunistic infections.

In summary, this study provides clinical evidence that early treatment with dexamethasone and antituberculosis drugs improves survival among patients over 14 years of age with tuberculous meningitis, regardless of disease severity. However, dexamethasone probably does not prevent severe disability in the survivors.

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