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ORIGINAL ARTICLE

Trial of Dexamethasone for Chronic Subdural Hematoma

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ABSTRACT

BACKGROUND

Chronic subdural hematoma is a common neurologic disorder that is especially prevalent among older people. The effect of dexamethasone on outcomes in patients with chronic subdural hematoma has not been well studied.

METHODS

We conducted a multicenter, randomized trial in the United Kingdom that enrolled adult patients with symptomatic chronic subdural hematoma. The patients were assigned in a 1:1 ratio to receive a 2-week tapering course of oral dexamethasone, starting at 8 mg twice daily, or placebo. The decision to surgically evacuate the hematoma was made by the treating clinician. The primary outcome was a score of 0 to 3, representing a favorable outcome, on the modified Rankin scale at 6 months after randomization; scores range from 0 (no symptoms) to 6 (death).

RESULTS

From August 2015 through November 2019, a total of 748 patients were included in the trial after randomization — 375 were assigned to the dexamethasone group and 373 to the placebo group. The mean age of the patients was 74 years, and 94% underwent surgery to evacuate their hematomas during the index admission; 60% in both groups had a score of 1 to 3 on the modified Rankin scale at admission. In a modified intention-to-treat analysis that excluded the patients who withdrew consent for participation in the trial or who were lost to follow-up, leaving a total of 680 patients, a favorable outcome was reported in 286 of 341 patients (83.9%) in the dexamethasone group and in 306 of 339 patients (90.3%) in the placebo group (difference, −6.4 percentage points [95% confidence interval, −11.4 to −1.4] in favor of the placebo group; P=0.01). Among the patients with available data, repeat surgery for recurrence of the hematoma was performed in 6 of 349 patients (1.7%) in the dexamethasone group and in 25 of 350 patients (7.1%) in the placebo group. More adverse events occurred in the dexamethasone group than in the placebo group.

CONCLUSIONS

Among adults with symptomatic chronic subdural hematoma, most of whom had undergone surgery to remove their hematomas during the index admission, treatment with dexamethasone resulted in fewer favorable outcomes and more adverse events than placebo at 6 months, but fewer repeat operations were performed in the dexamethasone group. (Funded by the National Institute for Health Research Health Technology Assessment Programme; Dex-CSDH ISRCTN number, ISRCTN80782810.)

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*A complete list of the British Neurosurgical Trainee Research Collaborative and Dex-CSDH Trial Collaborators is provided in the Supplementary Appendix, available at NEJM.org.

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Chronic subdural hematoma is a common neurologic disorder that affects mainly older people.[1] The disorder is characterized by a collection of blood and blood-breakdown products in the intracranial subdural space that liquefies over time. The inciting event is often minor head trauma, and subsequent inflammation may play a role in the pathogenesis.[2] The time of onset of chronic subdural hematoma is often not known. The incidence of chronic subdural hematoma is increasing owing to an aging population and the use of anticoagulant and antiplatelet medications.[3] Chronic subdural hematoma evacuation has been projected to become the most common cranial neurosurgical operation among adults by the year 2030 in the United States.[4]

Patients with chronic subdural hematoma often present with cognitive impairment, gait disturbance, limb weakness, or headache, and the diagnosis is made on the basis of cranial imaging.[5] Surgical evacuation of the subdural collection remains the main treatment approach for symptomatic patients; however, the hematoma recurs in 10 to 20% of surgically treated patients.[1,6]

Glucocorticoids have been used to treat chronic subdural hematoma.[7] Systematic reviews have concluded that glucocorticoids may be safe and effective when used in addition to surgery, with the aim of reducing the risk of recurrence, or as stand-alone therapy, with the aim of avoiding surgery.[8,9] However, there is limited evidence from multicenter, randomized trials to assess the effects of glucocorticoids on outcomes. We conducted a multicenter, randomized, placebo-controlled trial to assess the effect of dexamethasone on outcomes in patients with symptomatic chronic subdural hematoma.

Methods

Trial Design and Oversight

The Dexamethasone for Adult Patients with a Symptomatic Chronic Subdural Haematoma (Dex-CSDH) trial was a multicenter, randomized trial that was conducted in the United Kingdom. The trial compared a tapering 2-week course of dexamethasone with matching placebo in patients with symptomatic chronic subdural hematoma.[10] Ethical approval in the United Kingdom was obtained from the North-West Haydock Research and Ethics Committee in 2015. An internal pilot randomized trial, which enrolled 100 patients at seven trial sites, confirmed the operational feasibility of the overall trial.[11] As prespecified, the pilot phase did not aim to assess efficacy or reestimate the sample size, and these patients were included in the final analysis.

When possible, written informed consent was obtained from the patients or from their legal representative if they lacked the capacity to provide consent. If a patient was unable to provide consent and lacked a legal representative, agreement by an independent health care professional was necessary for enrollment. An independent trial steering committee and an independent data monitoring and ethics committee reviewed the trial every 6 to 12 months to assess conduct, progress, and safety.

The trial protocol was designed by neurosurgeons, neurologists, stroke physicians, and geriatricians from several hospitals and universities in the United Kingdom, with methodologic input from members of the Cambridge Clinical Trials Unit. Details of the protocol have been published previously[10] and are available with the full text of this article at NEJM.org. The investigators vouch for the completeness and accuracy of the data and analyses, for the complete reporting of adverse events, and for the fidelity of the trial to the protocol and statistical analysis plan (available with the protocol). The analysis was conducted by two authors from the Cambridge Clinical Trials Unit who are statisticians. The first draft of the manuscript was written by the first two authors and the last author and was revised by all the authors, who collectively agreed to submit the manuscript for publication.

Patients

Patients were eligible for enrollment if they were 18 years or age and older and were admitted to a participating neurosurgical unit with symptomatic chronic subdural hematoma that had been confirmed on cranial imaging. Trial sites were hospitals in the United Kingdom that provide emergency neurosurgical services 24 hours per day (Section S1 in the Supplementary Appendix, available at NEJM.org). A chronic subdural hematoma was defined pragmatically as a predominantly hypodense or isodense (relative to the brain) crescentic collection along the cerebral convexity on computed tomography (CT) of the head. Symptoms that were attributable to

a chronic subdural hematoma and met trial inclusion criteria included headache, gait disturbance, confusion or cognitive decline, limb weakness, speech disturbance, drowsiness or decreased consciousness, and seizures. Patients with mild or severe symptoms were enrolled; none of the enrolled patients were asymptomatic.

Patients were excluded if they had conditions for which glucocorticoids are contraindicated (e.g., active systemic infection, recent peptic ulceration or gastrointestinal bleeding), were receiving (or had been receiving within 1 month before screening) oral or intravenous glucocorticoids on a regular basis, were previously enrolled in this trial for a separate chronic subdural hematoma episode, had a cerebrospinal fluid shunt, had severe lactose intolerance or a known hypersensitivity to dexamethasone or other excipient, had a history of psychotic disorders, or were unwilling to take products containing gelatin. Patients were not eligible for randomization if they were not able to receive the first dose of the trial drug or placebo within 72 hours after admission to the neurosurgical unit. Patients with an acute hematoma, as indicated by a predominantly hyperdense (relative to the brain) subdural collection on a CT scan, were not eligible for randomization.

RANDOMIZATION

Patients were treated in neurosurgical units according to standard practice. In the United Kingdom, standard practice typically includes burr hole evacuation of the hematoma with the use of a subdural drain.[5] The decision to perform surgical evacuation of the subdural collection or conservative monitoring was made by the clinical team in conjunction with the patient. Enrollment took place irrespective of the decision to operate and the timing of the surgical intervention.

Eligible patients were randomly assigned in a 1:1 ratio to receive a tapering 2-week course of oral dexamethasone (8 mg twice daily on days 1 to 3, then 6 mg twice daily on days 4 to 6, then 4 mg twice daily on days 7 to 9, then 2 mg twice daily on days 10 to 12, and then 2 mg once daily on days 13 and 14) or matching placebo. If oral administration was not possible, the trial agent was administered in a nasogastric tube. Patients could complete the tapering course at home if they were discharged. Adherence was assessed by reviewing medication records and patient diaries if the medication was taken at home. Randomization was performed with the use of permuted blocks (random block sizes of two or four), with stratification according to trial site. An interactive Web-based response system was used for allocating treatment packs of 62 dexamethasone tablets (2 mg) or 62 placebo capsules, both overencapsulated to look identical. The assigned trial drug or placebo was administered as part of the routine drug round by unit nurses.

OUTCOMES

In keeping with previous studies of chronic subdural hematomas,[5,12] the primary outcome was a score of 0 to 3 on the modified Rankin scale at 6 months after randomization. The modified Rankin scale is an ordinal outcome scale of disability or dependence with respect to activities of daily living and was originally designed for use in patients with stroke but is used in patients with other disorders, including chronic subdural hematoma.[13,14] The scale has seven categories: no symptoms (0), no clinically significant disability despite symptoms (1), slight disability (2), moderate disability (3), moderately severe disability (4), severe disability (5), and death (6); in this trial, a score of 0 to 3 was used to represent a favorable outcome.

Our hypothesis was that dexamethasone would improve the 6-month functional outcome in patients with symptomatic chronic subdural hematoma by reducing the need for surgical interventions and recurrence of the hematoma after surgery. The scores on the modified Rankin scale were assessed with the use of a validated simplified questionnaire, which was completed by the patients or caregivers at 3 months and 6 months after randomization; if no response was received, a trial team member contacted the patient or caregiver by telephone to complete the questionnaire.[15] All completed questionnaires were reviewed at the coordinating center by a clinically trained investigator, who was unaware of the trial-group assignments; this investigator calculated the modified Rankin scale score according to a standardized algorithm (Section S3).

Secondary outcomes were the score on the modified Rankin scale at discharge from the neurosurgical unit and at 3 months after randomization; mortality at 30 days and 6 months

after randomization; the number of patients who underwent surgical interventions related to chronic subdural hematoma during the index admission; the number of patients who underwent surgical interventions related to chronic subdural hematoma during subsequent admissions in the follow-up period; the score on the Glasgow Coma Scale (scores range from 3 to 15, with higher scores indicating better neurologic status) at discharge and at 6 months; the score on the Barthel Index at discharge and at 3 months and 6 months after randomization (scores range from 0 to 100, with higher scores indicating a greater ability to complete activities of daily living)[16]; EuroQol Group 5-Dimension 5-Level questionnaire (EQ-5D-5L) utility index score at discharge and at 3 months and 6 months after randomization (responses on the EQ-5D-5L were converted into a utility index score with the use of the cross-walk algorithm; scores range from −0.594 [health state worse than death] to 1 [perfect health state] — patients who died were given a score of zero)[17,18]; length of stay in the neurosurgical unit; discharge destination from the neurosurgical unit; length of stay in secondary care; and adverse events. Postoperative recurrence of subdural hematoma was a tertiary outcome that was defined as a symptomatic recurrence leading to reoperation of a previously evacuated ipsilateral chronic subdural hematoma.[19] Adverse events of special interest included hyperglycemia leading to treatment or discontinuation of the trial regimen, new-onset diabetes, hyperosmolar hyperglycemic state, new-onset psychosis, peptic ulceration or gastrointestinal bleeding, and other upper gastrointestinal side effects.[10]

STATISTICAL ANALYSIS

Assuming a loss to follow-up of 15%, we estimated that a target sample size of 750 patients would provide the trial with a power of 81 to 92% (at a two-sided significance level of 5%) to detect a treatment effect of 8 percentage points, indicating an increase in the percentage of patients with a favorable outcome from between 80 and 85% to between 88 and 93%.[10] This difference of 8 percentage points was determined to be a clinically relevant treatment effect on the basis of estimates of a favorable outcome in 80 to 85% of patients in previous studies.[12] A prespecified blinded interim analysis of pooled outcome data was performed after 450 patients had completed 6 months of follow-up in order to decide if the sample size had to be adjusted. The possible alternatives after the interim analysis were to increase the sample size (with a maximum of 1000 patients) or to stop the trial for futility if the revised sample size was more than 1000 patients. Because the trial could only be stopped for futility, we did not adjust the confidence interval and P value at the end of the trial to account for the interim analysis. The independent data monitoring and ethics committee recommended that recruitment should continue to the original target sample size of 750 patients. The analysis was conducted according to a statistical analysis plan,[19] which was agreed on without reference to the unblinded data (see the protocol). No alpha-spending adjustment was required as a result of the 100-patient pilot trial, because this pilot phase was designed solely to determine the operational feasibility of continuing the trial.

Outcome analyses were performed in the modified intention-to-treat population, which included all randomly assigned patients except those who withdrew consent for participation in the trial and those lost to follow-up. Here we present the results of an analysis of the primary outcome, with a sensitivity analysis under missing-not-at-random assumptions, as described in Section S11.

The primary analysis estimated the absolute between-group difference in the percentage of patients who had a favorable outcome (i.e., a score of 0 to 3 on the modified Rankin scale at 6 months), under the assumption of a normal distribution and with the level of significance set at a two-sided P value of less than 0.05. As secondary analyses of the primary outcome, logistic-regression and proportional-odds logistic-regression (using the ordinal modified Rankin scale score[20]) analyses that adjusted for the baseline covariates of age and Glasgow Coma Scale score were planned; however, the proportional-odds logistic-regression analysis could not be performed because the proportionality assumption was violated. A sensitivity analysis was performed in the per-protocol population, which included all randomly assigned patients except those who received less than 80% of their assigned intervention or received more than 8 mg of dexamethasone if in the placebo group (e.g., for postoperative nausea and vomiting). There was

no plan for adjustment of confidence intervals for multiple comparisons of secondary outcomes, and these outcomes are reported as point estimates with confidence intervals that have not been adjusted for multiplicity and from which no clinical conclusions can be drawn.

Exploratory analyses were performed to examine the effect of interaction between treatment and prespecified subgroups on the primary outcome. Other exploratory analyses are listed in Section S6. Safety data on serious adverse events and adverse events of special interest collected in the first 30 days (Section S2) are presented as incidence rates and relative risks with 95% confidence intervals, classified according to system organ class in the *Medical Dictionary for Regulatory Activities* and stratified according to trial group. If the outcome of an adverse event of special interest was considered serious, then it was included in the serious adverse event group. A health economic analysis was prespecified in the trial protocol but has not yet been performed.

RESULTS

PATIENTS

From August 2015 through November 2018, patients were enrolled in the trial at 23 sites in the United Kingdom. A total of 2203 patients were screened for eligibility, and 750 patients were randomly assigned to a trial group. Two patients were excluded immediately after randomization owing to ineligibility; neither patient had received their assigned intervention, and no data were collected from these patients. Thus, 748 patients were enrolled in the trial — 375 in the dexamethasone group and 373 in the placebo group (Fig. 1). A total of 45 patients (20 in the dexamethasone group and 25 in the placebo group) withdrew their consent to participate in the trial, and 23 patients were lost to final follow-up (14 in the dexamethasone group and 9 in the placebo group). The remaining 680 patients, constituting the modified intention-to-treat population, were followed up for the primary outcome at 6 months (341 in the dexamethasone group and 339 in the placebo group). With respect to the primary outcome, data were missing for 9% of the patients (34 patients in each trial group). A similar amount of data were missing for the secondary outcomes.

The baseline characteristics were similar in the two trial groups, with 59.9% of the patients having a score of 1 to 3 on the modified Rankin scale and 94.3% having a score of 13 to 15 on the Glasgow Coma Scale at admission. Approximately 70% of the patients had a history of known head trauma. Fewer patients in the dexamethasone group than in the placebo group were independently mobile without any aids before they received their diagnosis of chronic subdural hematoma (Table 1 and Table S5). Atrial fibrillation was reported in 20.9% of the patients, and 46.6% of the patients were taking an antithrombotic medication at the time of diagnosis. The imaging characteristics of chronic subdural hematoma were similar in the two trial groups.

Among the 742 patients who could be evaluated, 699 (94.2%) underwent surgical evacuation of the hematoma that was present during the initial admission, when they underwent randomization; surgery was performed either during the index admission (683 patients [342 in the dexamethasone group and 341 in the placebo group]) or during a subsequent admission (16 patients [5 in the dexamethasone group and 11 in the placebo group]). The surgical techniques used for evacuation of the subdural hematoma and adherence to the assigned regimen were similar in the trial groups (Table S5). Nasogastric tube administration of dexamethasone was reported in 6 of 375 patients in the dexamethasone group and in 4 of 373 patients in the placebo group.

PRIMARY OUTCOME

In the modified intention-to-treat analysis, a favorable outcome (a score of 0 to 3 on the modified Rankin scale) was reported in 286 of 341 patients (83.9%) in the dexamethasone group and in 306 of 339 patients (90.3%) in the placebo group at 6 months, for a between-group difference of −6.4 percentage points (95% confidence interval [CI], −11.4 to −1.4) in favor of the placebo group ($P=0.01$) (Table 2). The ordinal outcomes of the modified Rankin scale in each trial group at 6 months after randomization are provided in Table 2, and the dichotomous scores at discharge and at 3 months and 6 months after randomization are provided in Figure 2. After adjustment for prespecified covariates of age and Glasgow Coma Scale score at admission, the odds ratio for a favorable outcome with dexamethasone was 0.55 (95% CI, 0.33 to 0.91) in

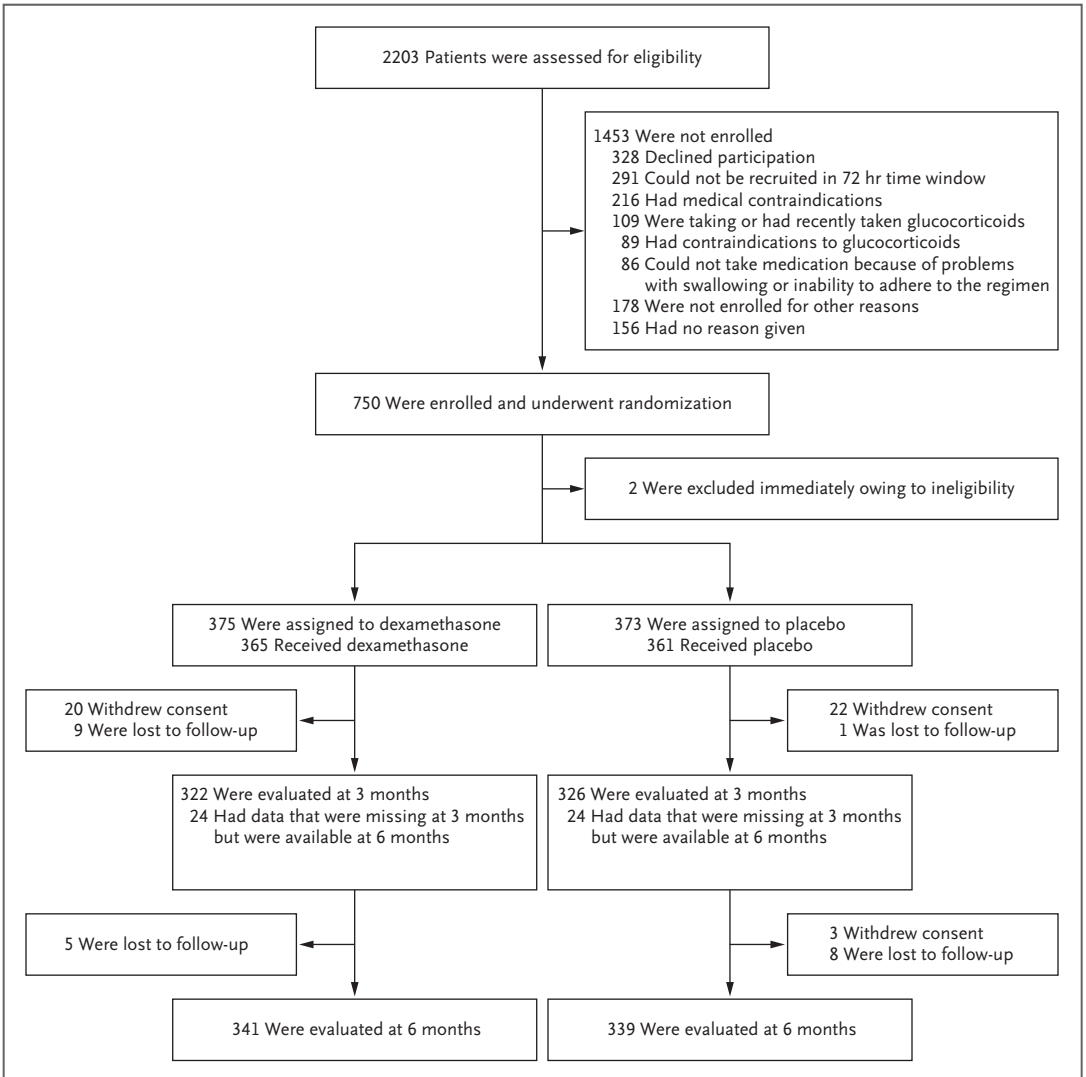

Figure 1. Screening, Randomization, and Follow-up.

favor of the placebo group (P=0.02). In the per-protocol analysis, a favorable outcome was reported in 229 of 270 patients (84.8%) in the dexamethasone group and in 258 of 283 patients (91.2%) in the placebo group at 6 months, for a between-group difference of −6.4 percentage points (95% CI, −12.0 to −0.97) in favor of the placebo group (P=0.02).

SECONDARY AND TERTIARY OUTCOMES

At 3 months, a favorable outcome was reported in 268 of 322 patients (83.2%) in the dexamethasone group and in 298 of 326 patients (91.4%) in the placebo group, for a between-group difference of −8.2 percentage points (95% CI, −13.3 to −3.1) in favor of the placebo group. The percentage of patients who underwent one operation for their chronic subdural hematoma during the index admission was 91.7% in dexamethasone group and 89.2% in placebo group. During subsequent admissions, 19 of 372 patients (5.1%) in the dexamethasone group and 28 of 370 patients (7.6%) in the placebo group underwent surgery related to the hematoma. Repeat surgery for recurrence of chronic subdural hematoma was performed in 6 of 349 patients (1.7%) in the

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Dexamethasone (N=375)	Placebo (N=373)
Age — yr	74.5±11.8	74.3±11
Male sex — no./total no. (%)	268/375 (71.5)	286/373 (76.7)
Symptoms at presentation — no./total no. (%)†		
Headache	211/373 (56.6)	214/373 (57.4)
Gait disturbance	171/373 (45.8)	170/373 (45.6)
Cognitive impairment	129/373 (34.6)	128/373 (34.3)
Hemiparesis	105/373 (28.2)	107/373 (28.7)
Speech disturbance	81/373 (21.7)	94/373 (25.2)
Seizure	11/373 (2.9)	10/373 (2.7)
Other	54/373 (14.5)	66/373 (17.7)
Modified Rankin scale score at admission — no./total no. (%)‡		
1–3	186/310 (60.0)	182/304 (59.9)
4–5	124/310 (40.0)	122/304 (40.1)
Glasgow Coma Scale score at admission — no./total no. (%)§		
13–15	350/371 (94.3)	350/371 (94.3)
9–12	15/371 (4.0)	15/371 (4.0)
3–8	6/371 (1.6)	6/371 (1.6)
Known head trauma — no./total no. (%)	253/373 (67.8)	267/373 (71.6)
Main coexisting medical conditions — no./total no. (%)		
Atrial fibrillation	88/375 (23.5)	68/373 (18.2)
Diabetes	55/375 (14.7)	54/373 (14.5)
Ischemic heart disease	58/375 (15.5)	50/373 (13.4)
Previous stroke	34/375 (9.1)	39/373 (10.5)
Any antithrombotic medication — no./total no. (%)	178/370 (48.1)	166/368 (45.1)
Midline shift on admission scan — no./total no. (%)		
0–5 mm	68/314 (21.7)	74/318 (23.3)
6–10 mm	126/314 (40.1)	115/318 (36.2)
>10 mm	120/314 (38.2)	129/318 (40.6)

* Plus–minus values are means ±SD. There were no clinically significant between-group differences in these baseline characteristics except for mobility before chronic subdural hematoma diagnosis. Total numbers of patients that are less than 375 in the dexamethasone group and 373 in the placebo group indicate that data were missing for some patients. Percentages may not total 100 because of rounding. Additional baseline data are provided in Section S4 in the Supplementary Appendix.
† Patients often had more than one symptom at presentation.
‡ Scores on the modified Rankin scale range from 0 (no symptoms) to 6 (death).
§ Scores on the Glasgow Coma Scale range from 3 to 15, with higher scores indicating better clinical status.

dexamethasone group and in 25 of 350 patients (7.1%) in the placebo group, for a between-group difference of 5.4 percentage points in favor of the dexamethasone group; 4 patients underwent multiple operations (1 in the dexamethasone group and 3 in the placebo group).

Adverse events of special interest occurred in 41 of 375 patients (10.9%) in the dexamethasone group and in 12 of 373 patients (3.2%) in the placebo group (odds ratio, 3.4 [95% CI, 1.81 to 6.85]), and serious adverse events occurred in 60 of 375 (16.0%) and 24 of 373 (6.4%), respec-

Table 2. Efficacy and Safety Outcomes.*

Variable	Dexamethasone	Placebo	Measure of Effect†	Difference or Odds or Rate Ratio (95% CI)	P Value
Primary outcome					
Modified Rankin scale score at 6 mo — no./total no. (%)					
Dichotomous outcomes					
0–3: Primary outcome	286/341 (83.9)	306/339 (90.3)	Percentage-point difference	−6.4 (−11.4 to −1.4)	0.01
4–6	55/341 (16.1)	33/339 (9.7)			
Ordinal outcomes					
0: No symptoms	163/341 (47.8)	164/339 (48.4)			
1: No clinically significant disability	49/341 (14.4)	55/339 (16.2)			
2: Slight disability	14/341 (4.1)	21/339 (6.2)			
3: Moderate disability	60/341 (17.6)	66/339 (19.5)			
4: Moderately severe disability	10/341 (2.9)	9/339 (2.7)			
5: Severe disability	15/341 (4.4)	7/339 (2.1)			
6: Dead	30/341 (8.8)	17/339 (5.0)			
Secondary, tertiary, and safety outcomes					
Modified Rankin scale score at 3 mo — no./total no. (%)					
0–3	268/322 (83.2)	298/326 (91.4)	Percentage-point difference	−8.2 (−13.3 to −3.1)	
4–6	54/322 (16.8)	28/326 (8.6)			
Modified Rankin scale score at discharge — no./total no. (%)					
0–3	255/318 (80.2)	263/316 (83.2)	Percentage-point difference	−3.0 (−9.1 to 3.0)	
4–6	63/318 (19.8)	53/316 (16.8)			
Mortality at 30 days — no./total no. (%)	8/375 (2.1)	2/373 (0.5)	Odds ratio	4.08 (1.01 to 27.2)	
Mortality at 6 mo — no./total no. (%)	30/341 (8.8)	17/339 (5.0)	Odds ratio	1.83 (0.99 to 3.45)	
One operation during index admission — no./total no. (%)	341/372 (91.7)	330/370 (89.2)	Rate ratio‡	0.97 (0.83 to 1.12)	
Operations during subsequent admissions — no./total no. (%)	19/372 (5.1)	28/370 (7.6)	Rate ratio‡	0.90 (0.72 to 1.11)	
Repeat surgery for recurrence of chronic subdural hematoma — no./total (%)§	6/349 (1.7)	25/350 (7.1)	Percentage-point difference	−5.4 (−8.7 to −2.5)	
Mean EQ-5D-5L utility index score¶					
At discharge	0.697	0.727	Difference	−0.03 (−0.07 to 0.01)	
At 3 mo	0.707	0.773	Difference	−0.07 (−0.12 to −0.02)	
At 6 mo	0.733	0.766	Difference	−0.03 (−0.09 to 0.02)	
Adverse events of special interest up to day 30 — no./total no. (%)‖	41/375 (10.9)	12/373 (3.2)	Odds ratio	3.40 (1.81 to 6.85)	<0.001
Serious adverse events up to day 30 — no./total no. (%)‖	60/375 (16.0)	24/373 (6.4)	Odds ratio	2.49 (1.54 to 4.15)	<0.001

Table 2. (Continued.)

* Because of the lack of a prespecified plan for adjusting confidence intervals for multiple comparisons, no definite conclusions can be drawn from secondary outcome data in the trial. Percentages may not total 100 because of rounding.
† Between-group differences were calculated as the value in the dexamethasone group minus the value in the placebo group, and odds ratios are shown for the dexamethasone group as compared with the placebo group.
‡ Data were missing for 3 patients in dexamethasone group and 3 patients in placebo group. Additional data are provided in Section S7 in the Supplementary Appendix. The number of operations were analyzed with the use of a Poisson regression model, which provides an estimate of the ratio of the mean number of operations between the trial groups; a value of less than 1 indicates fewer operations occurred in the dexamethasone group.
§ A total of 43 patients underwent more than one cranial surgery during the trial period. Among these 43 patients, repeat surgery was performed in 31 for recurrent chronic subdural hematoma, in 10 for empyema (1 of the 10 patients who underwent repeat surgery for empyema also had undergone repeat surgery for a previous recurrence of chronic subdural hematoma), in 2 for expansion of contralateral side chronic subdural hematoma, and in 1 for postoperative acute subdural hematoma. The time interval to the first repeat surgery for recurrence of chronic subdural hematoma was a mean of 18 days and a median of 14 days.
¶ The responses on the EuroQol Group 5-Dimension 5-Level questionnaire (EQ-5D-5L) were converted into a utility index score with the use of the cross-walk algorithm; scores range from –0.594 [health state worse than death] to 1 [perfect health state] — patients who died were given a score of zero. Linear regression was used to estimate the treatment effect and 95% confidence interval.
‖ Additional data on adverse events of special interest and serious adverse events are provided in Sections S8 and S9.

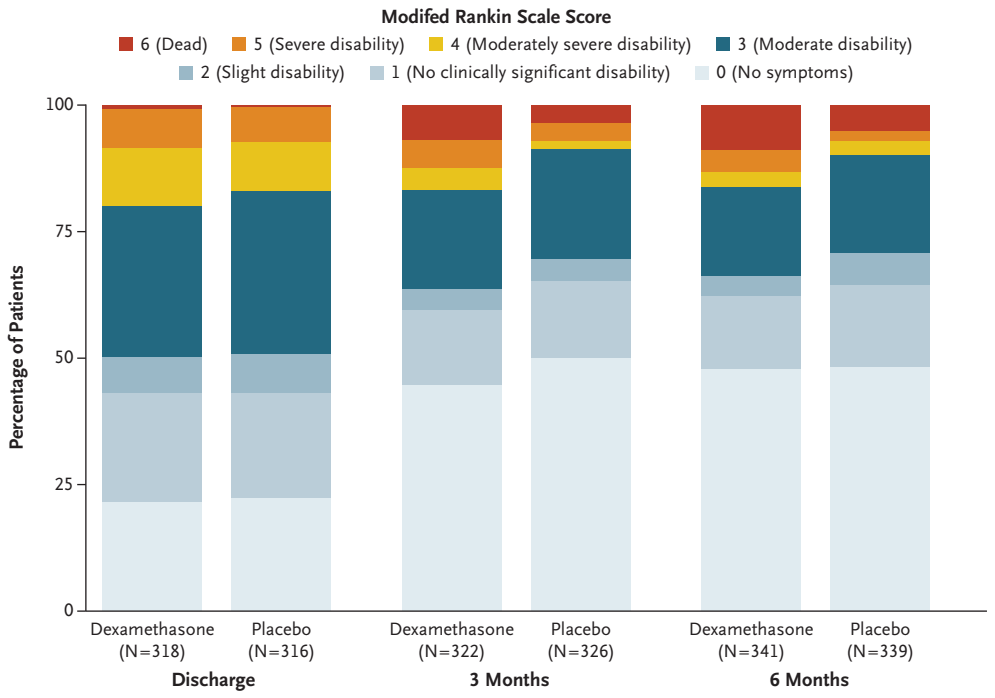

Figure 2. Modified Rankin Scale Score at Discharge and at 3 Months and 6 Months after Randomization.
The proportionality assumption was not upheld, and common odds ratios could not be calculated.

tively (odds ratio, 2.49 [95% CI, 1.54 to 4.15]). The risk of any infection was 6.4% in the dexamethasone group and 1.1% in the placebo group. Among the 699 patients who could be evaluated, 12 (1.7% [8 in the dexamethasone group and 4 in placebo group]) had a surgical site infection — 2 patients had a superficial wound infection and 10 had a subdural empyema. The results for the remaining secondary outcomes, including mortality, EQ-5D-5L utility

index score, length of stay, and discharge destination, are provided in Table 2 and Table S7.

The results of exploratory subgroup analyses are provided in Table S6. Among the 38 patients who received conservative management (i.e., those who did not undergo surgical evacuation of the hematoma that was evident on initial admission), a favorable outcome was reported in 18 of 22 patients (82%) in the dexamethasone group and in 16 of 16 patients (100%) in the placebo group.

DISCUSSION

In this trial involving patients with symptomatic chronic subdural hematoma, we found that the percentage of patients who had a favorable outcome (defined as a score of 0 to 3 on the modified Rankin scale at 6 months) was lower among those who received a 14-day tapering course of dexamethasone than among those who received placebo. Surgical evacuation of the chronic subdural hematoma was performed in 94% of the patients during the trial period, a percentage that is similar to that reported in a previous prospective, multicenter, observational study in the United Kingdom.[5] At admission, 60% of the patients had a score of 1 to 3 on the modified Rankin scale, and at 6 months, 87% of the patients had a score of 0 to 3; these findings are also in accordance with the results of prospective studies.[5,12]

We hypothesized that dexamethasone, as compared with placebo, would improve outcomes in patients with symptomatic chronic subdural hematoma by leading to clinical improvement that was adequate to enable nonoperative management and by reducing the risk of recurrence of the hematoma in patients who had undergone surgery.[21-24] However, contrary to our hypothesis, the result with respect to the primary outcome, a favorable outcome at 6 months, was worse in the dexamethasone group. Although the between-group difference of 6.4 percentage points was below the 8 percentage-point difference used in the power calculation, this difference may be clinically relevant and may suggest harm associated with dexamethasone with regard to a favorable outcome on the modified Rankin scale. Because almost all the patients underwent an initial operation to remove the hematoma, no firm conclusions could be drawn regarding the effect of dexamethasone as a method of conservative management to avoid surgery. The percentage of patients who underwent reoperation because of a recurrence of chronic subdural hematoma was 5.4 percentage points lower in the dexamethasone group than in the placebo group.

The treatment regimen consisted of a total 124 mg of dexamethasone administered as a tapering course over 14 days. The dosage and treatment duration in this trial were selected on the basis of previous studies[8] and are similar to the dosage and treatment duration used in other ongoing trials of glucocorticoids, although longer treatment durations of 3 and 8 weeks are also being evaluated.[25] The median time to recurrence of chronic subdural hematoma after surgical evacuation has been 12 to 15 days in several studies, and this was the rationale for designing the trial with a 2-week treatment period with dexamethasone.[5,12] More adverse events, such as hyperglycemia, new-onset diabetes, new-onset psychosis, and infections, were reported in the dexamethasone group than in the placebo group in our trial. It is possible that a shorter course with a smaller dose could reduce these risks.

A previous randomized, controlled trial that involved 20 patients at a single center assessed a 3-week course of dexamethasone at a dose of 12 mg per day, followed by a tapering course of dexamethasone, as treatment for asymptomatic or minimally symptomatic chronic subdural hematoma.[26] During the 6-month follow-up, surgical intervention in that trial had to be performed in 4 patients, of whom 3 were in the placebo group. There were more serious adverse events in the dexamethasone group than in the placebo group. Our trial was larger, enrolled a different patient population, and had a shorter duration of treatment, but we also observed that the percentage of patients with adverse events was higher in the dexamethasone group than in the placebo group.

Our trial has limitations. First, the majority of patients were treated surgically during their index admission, which limits our ability to draw conclusions regarding patients in whom the intention is to initially manage the subdural collection conservatively. The results of the exploratory subgroup analysis of the small number of patients who received nonoperative management, however, were in the same direction of effect as

the results of the primary analysis. Second, loss to follow-up at 6 months was 9%. Our sample-size calculation had allowed for up to 15% loss to follow-up, and the percentage was similar in the two trial groups. Third, owing to the characteristic adverse effects of dexamethasone, the clinical teams and patients may have become aware of the trial-group assignment. Finally, follow-up imaging was not mandated as part of the trial, and the trial outcomes did not include imaging results to address the possible effect of dexamethasone on the size of chronic subdural hematomas. This was not believed to be necessary in a pragmatic trial, and there is evidence that routine follow-up imaging after surgical evacuation of chronic subdural hematoma is not beneficial with regard to the score on the modified Rankin scale at 6 months.[27]

In this trial involving patients with chronic subdural hematoma, most of whom had undergone surgical evacuation during the index admission, treatment with dexamethasone resulted in a fewer favorable outcomes than placebo at 6 months, but fewer repeat operations for reaccumulation of the subdural collection were performed among the patients who received dexamethasone. Dexamethasone was associated with more adverse events than placebo.

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A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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APPENDIX

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