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ORIGINAL ARTICLE

Dexamethasone versus Surgery for Chronic Subdural Hematoma

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ABSTRACT

BACKGROUND

The role of glucocorticoids without surgical evacuation in the treatment of chronic subdural hematoma is unclear.

METHODS

In this multicenter, open-label, controlled, noninferiority trial, we randomly assigned symptomatic patients with chronic subdural hematoma in a 1:1 ratio to a 19-day tapering course of dexamethasone or to burr-hole drainage. The primary end point was the functional outcome at 3 months after randomization, as assessed by the score on the modified Rankin scale (range, 0 [no symptoms] to 6 [death]). Noninferiority was defined by a lower limit of the 95% confidence interval of the odds ratio for a better functional outcome with dexamethasone than with surgery of 0.9 or more. Secondary end points included scores on the Markwalder Grading Scale of symptom severity and on the Extended Glasgow Outcome Scale.

RESULTS

From September 2016 through February 2021, we enrolled 252 patients of a planned sample size of 420; 127 were assigned to the dexamethasone group and 125 to the surgery group. The mean age of the patients was 74 years, and 77% were men. The trial was terminated early by the data and safety monitoring board owing to safety and outcome concerns in the dexamethasone group. The adjusted common odds ratio for a lower (better) score on the modified Rankin scale at 3 months with dexamethasone than with surgery was 0.55 (95% confidence interval, 0.34 to 0.90), which failed to show noninferiority of dexamethasone. The scores on the Markwalder Grading Scale and Extended Glasgow Outcome Scale were generally supportive of the results of the primary analysis. Complications occurred in 59% of the patients in the dexamethasone group and 32% of those in the surgery group, and additional surgery was performed in 55% and 6%, respectively.

CONCLUSIONS

In a trial that involved patients with chronic subdural hematoma and that was stopped early, dexamethasone treatment was not found to be noninferior to burr-hole drainage with respect to functional outcomes and was associated with more complications and a greater likelihood of later surgery. (Funded by the Netherlands Organization for Health Research and Development and others; DECSA EudraCT number, 2015-001563-39.)

Chronic subdural hematoma is a common disorder and has been increasing in prevalence owing to the aging of the population and the widespread use of anticoagulant medication.[1,2] Minor head trauma often precedes the development of the hematoma; however, the disorder can occur in the absence of trauma. It has been postulated that an inflammatory response occurs in the subdural space in reaction to fluid collection,[3,4] which leads to expansion of the clot and clinical symptoms.[5]

Surgical evacuation of the hematoma by means of burr-hole craniostomy, often combined with placement of a subdural or subperiosteal drain, is the mainstay of treatment in symptomatic patients.[6,7] Albeit effective, surgical drainage carries a risk of death, and up to 10% of patients have recurrence of the subdural collection of fluid.[6,8] Glucocorticoid therapy has been proposed as an alternative, nonoperative treatment for chronic subdural hematoma. Dexamethasone has the potential to block inflammatory changes in the subdural space, thereby impeding hematoma persistence and growth, and is administered to patients for this purpose in some institutions.[9]

Although studies and systematic reviews have shown that glucocorticoids were safe and may be effective as therapy for chronic subdural hematoma, a recent randomized trial showed that dexamethasone resulted in fewer favorable outcomes and more adverse events than placebo.[10] In that trial, however, most patients had undergone surgical evacuation during the index admission. Whether dexamethasone without initial surgery has the same potential as surgery alone to achieve favorable outcomes in patients with chronic subdural hematoma remains unclear. We conducted a multicenter, open-label, randomized, controlled, noninferiority trial to compare dexamethasone treatment as stand-alone therapy and surgical evacuation for symptomatic chronic subdural hematoma.

METHODS

TRIAL DESIGN AND OVERSIGHT

The Dexamethasone Therapy versus Surgery for Chronic Subdural Hematoma (DECSA) trial was an investigator-initiated, multicenter, randomized trial, designed according to the Prospective Randomized Open Blinded End-Point (PROBE) trial design.[11] The trial was conducted at 12 hospitals in the Netherlands (Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). Details of the protocol have been published previously,[12] and the protocol is available at NEJM.org.

A Quick Take is available at NEJM.org

The trial was conducted in accordance with International Council for Harmonisation guidelines and the ethical principles of the Declaration of Helsinki. Written informed consent was obtained from the patients or from their legal representatives if they lacked the capacity to provide consent. The trial steering committee met approximately every 6 weeks to discuss the conduct, progress, and safety of the trial (Table S2). Data from case-record forms were monitored yearly by independent external experts throughout the trial to verify adherence to the protocol and the completeness, consistency, and accuracy of the data. An independent data and safety monitoring board reviewed the trial according to a charter for trial safety and efficacy; a detailed description of the charter is provided in the Supplementary Appendix. Prespecified interim analyses of major end points, including serious adverse events, were planned after the inclusion of 150 and 300 patients. After the interim analysis of data of the first 150 patients who had completed the 3-month follow-up period, the data and safety monitoring board requested an unplanned additional review of all enrolled patients. This analysis resulted in premature termination of the trial because the outcomes were considered to be worse and the incidences of complications were higher in the dexamethasone group. We report results with respect to the primary and secondary end points in an analysis involving all included patients at 3 months of follow-up.

The trial protocol was written by the first two authors, with guidance from the last three authors in collaboration with neurologists and neurosurgeons from seven hospitals in the Netherlands. Methodologic input was provided by the Department of Public Health and Medical Decision Making of the Erasmus Medical Center. The first draft of the manuscript was written by the first two authors and the last three authors and was revised by all the authors, including the collaborators, who collectively agreed to submit the manuscript for publication. The investigators vouch for the completeness and accuracy of the

data, for the complete reporting of adverse events, and for the adherence of the trial to the protocol. The trial sponsors (three nonprofit organizations) had no involvement in the trial design, trial conduct, protocol review, or manuscript preparation or review.

PATIENTS

We recruited patients 18 years of age or older from the outpatient clinics and emergency departments of participating hospitals who had newly diagnosed symptomatic chronic subdural hematoma detected on computed tomography (CT). Chronic subdural hematoma was defined as a predominantly hypodense or isodense collection of fluid (relative to brain parenchyma) in the subdural space. For inclusion, patients had to have clinical symptoms attributable to the chronic subdural hematoma, as judged by the treating physician, and have a symptom severity score on the Markwalder Grading Scale of 1 (headache only), 2 (moderate focal neurologic deficit), or 3 (severe focal neurologic deficit). The Markwalder Grading Scale is a system for assessing chronic subdural hematoma; scores range from 0 (asymptomatic) to 4 (coma with a lack of motor responses to painful stimuli).[13] Patients were not eligible for enrollment if they had an acute subdural hematoma (defined as a predominantly hyperdense subdural collection of fluid on CT), were asymptomatic or comatose, had poorly regulated diabetes mellitus (defined as a glycated hemoglobin level >8% [64 mmol per mole]), had glaucoma, were pregnant, had received a cerebrospinal fluid shunt, or had contraindications to glucocorticoids.

TRIAL PROCEDURES

Patients were randomly assigned in a 1:1 ratio to the dexamethasone group or the surgery group, with stratification according to trial site. Balanced random samples were generated through block randomization with the use of a computer randomization algorithm. For all included patients, antithrombotic therapies were discontinued on the day of randomization. Previous use of antithrombotic agents was not included in the randomization algorithm.

Dexamethasone was administered orally, or intravenously when oral administration was not possible, in a 19-day tapering course (8 mg every 12 hours on days 1 through 4, tapered by half every 3 days until 0.5 mg per day on day 19, and stopped on day 20). For the surgery group, evacuation of the subdural collection was scheduled within 7 days after randomization to provide a safe interval in case of antithrombotic-therapy use. In all participating hospitals, the standard surgical treatment was burr-hole evacuation of the hematoma, followed by insertion of a subdural drain for 2 days. Preoperative antibiotic prophylaxis was administered, and either general or local anesthesia could be used according to local practice. All the patients underwent follow-up CT at 2 weeks after the initiation of treatment.

Discontinuation of dexamethasone therapy before the completion of treatment was indicated in case of a lack of improvement at 2 weeks (i.e., if the patient had the same score on the Markwalder Grading Scale as at baseline or had a higher score than at baseline) or an increase in hematoma size on follow-up CT. Other reasons for discontinuation of dexamethasone were clinical deterioration (defined as an increase of ≥1 point in the score on the Markwalder Grading Scale) at any time after initiation of treatment or the occurrence of severe, dexamethasone-related side effects or complications. Patients with bilateral chronic subdural hematomas could be included in the analysis, with the index lesion considered to be on the side that created midline shift to the opposite side. The definition of a lack of improvement in patients with bilateral chronic subdural hematoma was the same as that for patients with unilateral chronic subdural hematoma. If dexamethasone was discontinued, the patients could receive surgical treatment by burr-hole drainage. Reoperation after initial surgical treatment was indicated when neurologic deficits did not resolve, deteriorated, or recurred within the follow-up period and CT showed residual or recurrent hematoma, but reoperation was at the discretion of the treating physician, who was aware of the trial-group assignments. Reoperation to remove residual hematoma was generally similar to the original surgery or could be more extensive at the discretion of the treating surgeon.

END POINTS

The primary end point was the functional outcome at 3 months after randomization, as assessed by the score on the modified Rankin

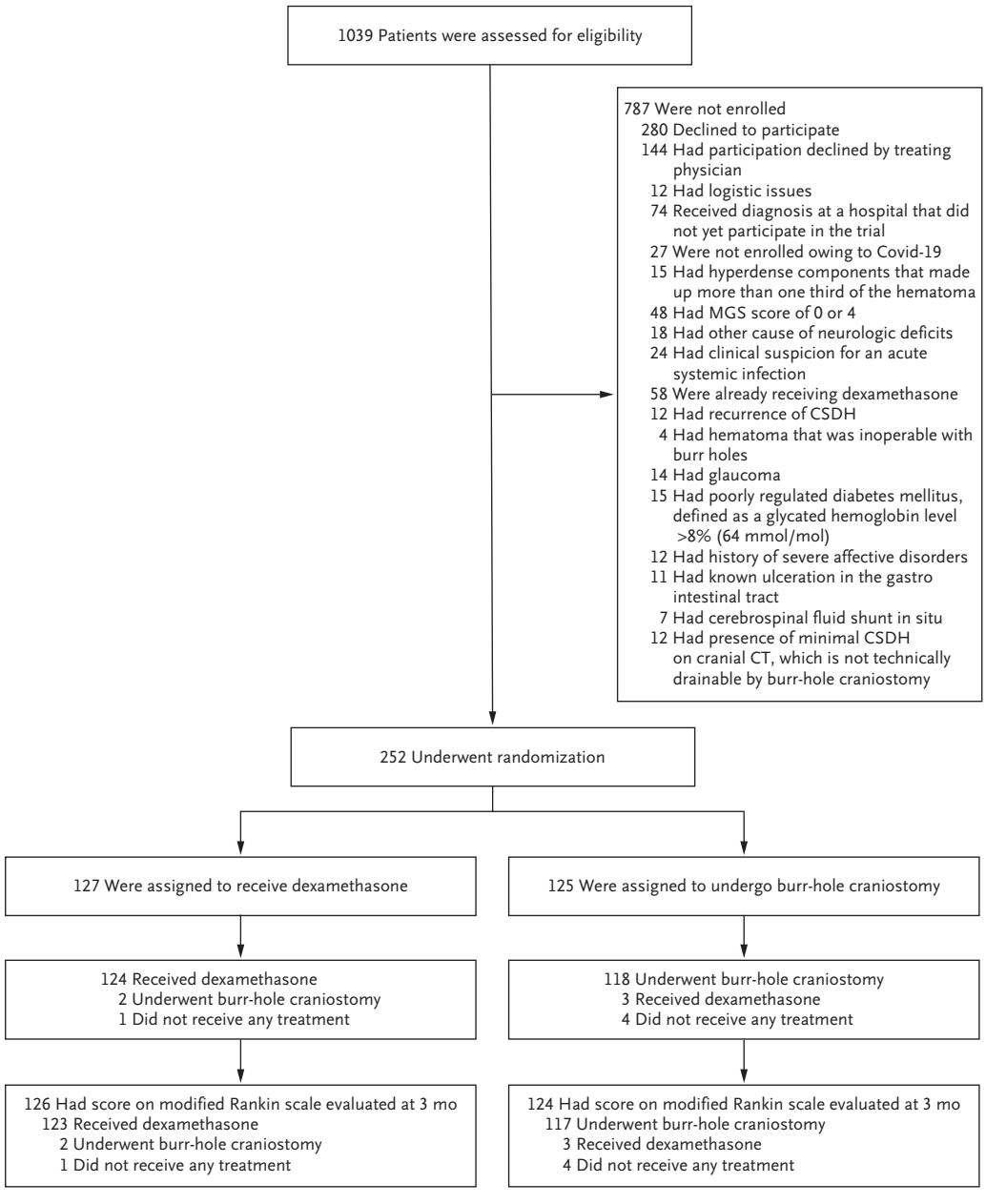

Figure 1. Screening, Randomization, and Follow-up.

The Markwalder Grading Scale (MGS) is a system for assessing chronic subdural hematoma; scores range from 0 (asymptomatic) to 4 (coma with a lack of motor responses to painful stimuli). Covid-19 denotes coronavirus disease 2019, and CSDH chronic subdural hematoma.

scale. A score of 0 indicates no symptoms, 1 no clinically significant disability despite symptoms, 2 slight disability, 3 moderate disability, 4 moderately severe disability, 5 severe disability, and 6 death.[13] Trained research nurses, who were unaware of the trial-group assignments, assessed scores on the modified Rankin scale according to a standardized algorithm by telephone at 3 months.

Secondary end points were the score on the

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Dexamethasone (N=127)	Surgery (N=125)
Age — yr	75.4±10.2	73.5±11.1
Male sex — no. (%)	99 (78.0)	96 (76.8)
Symptoms at presentation — no. (%)		
Headache	65 (51.2)	66 (52.8)
Gait disturbance	89 (70.1)	74 (59.2)
Altered mental status	81 (63.8)	62 (49.6)
Hemiparesis	86 (67.7)	61 (48.8)
Speech disorder	41 (32.3)	29 (23.2)
Seizure	9 (7.1)	2 (1.6)
Nausea or vomiting	13 (10.2)	14 (11.2)
Other	58 (45.7)	44 (35.2)
Score on modified Rankin scale at admission — no. (%)†		
0: No symptoms	0	0
1: No clinically significant disability	14 (11.0)	17 (13.6)
2: Slight disability	18 (14.2)	40 (32.0)
3: Moderate disability	16 (12.6)	23 (18.4)
4: Moderately severe disability	73 (57.5)	42 (33.6)
5: Severe disability	6 (4.7)	3 (2.4)
Score on Markwalder Grading Scale at admission — no. (%)‡		
1: Alert, oriented; mild symptoms such as headache	33 (26.0)	59 (47.2)
2: Drowsy or disoriented with variable deficits	93 (73.2)	65 (52.0)
3: Stuporous; responding to stimuli, severe focal signs	1 (0.8)	1 (0.8)
Known head trauma — no. (%)	95 (74.8)	95 (76.0)
Main coexisting medical condition — no. (%)		
None	7 (5.5)	7 (5.6)
Atrial fibrillation	30 (23.6)	24 (19.2)
Diabetes§	22 (17.3)	24 (19.2)
Ischemic heart disease	28 (22.0)	12 (9.6)
Previous stroke	23 (18.1)	24 (19.2)
Other	17 (13.4)	34 (27.2)
Any antithrombotic medication — no. (%)	77 (60.6)	65 (52.0)
Bilateral CSDH on CT — no. (%)	43 (33.9)	33 (26.4)
Midline shift in unilateral CSDH on admission CT		
Mean — mm	9.2±3.9	9.0±3.8
Distribution — no./total no. (%)		
0–5 mm	13/84 (15)	14/92 (15)
6–10 mm	34/84 (40)	42/92 (46)
>10 mm	37/84 (44)	36/92 (39)
Hematoma volume on admission CT		
Hematoma on left side — ml		
Mean	116.0±66.0	118.0±70.1
Range¶	6.0–360.6	10.7–373.1

Table 1. (Continued.)

Characteristic	Dexamethasone (N=127)	Surgery (N=125)
Hematoma on right side — ml		
Mean	119.6±66.1	107.9±51.3
Range¶	4.0–281.9	2.7–225.1

* Plus–minus values are means ±SD. Data on race were not collected; details on the representativeness of the trial population are provided in Table S4 in the Supplementary Appendix. CSDH denotes chronic subdural hematoma.
† Scores on the modified Rankin scale range from 0 (no symptoms) to 6 (death).
‡ The Markwalder Grading Scale is a system for assessing chronic subdural hematoma; scores range from 0 (asymptomatic) to 4 (coma with a lack of motor responses to painful stimuli). Patients with a score of 0 or 4 were not eligible for the trial.
§ Patients with a glycated hemoglobin level of more than 8% (64 mmol per mole) were excluded from the trial.
¶ Bilateral hematomas were included in this analysis. The smallest unilateral volume was 4.0 ml in the dexamethasone group and 2.7 ml in the surgery group.

modified Rankin scale at discharge and at 2 weeks; the score on the Markwalder Grading Scale at discharge, 2 weeks, and 3 months after randomization; the score on the Extended Glasgow Outcome Scale (range, 1 [death] to 8 [upper good recovery]) at 3 months; hematoma thickness (in millimeters) at 2 weeks; symptomatic residual or recurrent hematoma on follow-up CT resulting in additional intervention within 3 months after index treatment; overall complications, including drug-related adverse events; overall length of hospital stay within 3 months; and death at 3 months.

STATISTICAL ANALYSIS

We designed the trial to determine whether dexamethasone was noninferior to surgery with respect to functional outcomes on the modified Rankin scale at 3 months. Assuming that the true effect of dexamethasone as compared with surgery would result in a proportional odds ratio of 1.15 for a lower (better) score on the modified Rankin scale with dexamethasone, with the odds ratio estimated by means of proportional-odds regression, we aimed to include 420 patients to attain a power of 90% (see the protocol for details). Noninferiority would be established if the lower limit of the 95% confidence interval of the odds ratio for a better functional outcome with dexamethasone than with surgery was equal to or greater than 0.9. The trial was designed with a one-sided hypothesis test for the primary end point at an alpha level of 0.025. Further details are provided in the statistical analysis plan, available with the protocol.

The primary analysis consisted of estimating the adjusted common odds ratio for a shift in the direction of a lower score on the modified Rankin scale. The odds ratio was estimated on a modified intention-to-treat basis with a multivariable proportional-odds logistic regression with adjustment for the covariates prespecified in the protocol, including baseline scores on the modified Rankin scale and the Markwalder Grading Scale. Patients with missing outcomes were excluded. For secondary end points, ordinal outcomes were analyzed with proportional-odds logistic regression, and binary outcomes were analyzed with binary logistic regression. Because the statistical analysis plan did not include a provision for correcting the widths of confidence intervals for multiplicity when conducting tests for secondary end points, results are reported as point estimates and 95% confidence intervals, and no definite conclusions can be drawn from these results. Given the smaller sample size than originally anticipated because of premature discontinuation of the trial, we did not perform any subgroup analysis. We used RStudio statistical software (version 1.1.463) for all analyses.

RESULTS

TRIAL PATIENTS

After an interim analysis involving 252 enrolled patients, the trial was terminated early by the data and safety monitoring board owing to safety and outcome concerns with dexamethasone. From September 2016 through February 2021, a total of 1039 patients were screened (Fig. 1). At the time of cessation of the trial, 252

Table 2. Primary and Secondary End Points.*

Variable	Dexamethasone (N=127)	Surgery (N=125)	Measure of Effect	Difference or Odds Ratio (95% CI)
Primary end point				
Score on modified Rankin scale at 3 mo — no./total no. (%)			Adjusted common odds ratio†	0.55 (0.34–0.90)
0: No symptoms	22/126 (17.5)	44/124 (35.5)		
1: No clinically significant disability	33/126 (26.2)	41/124 (33.1)		
2: Slight disability	26/126 (20.6)	12/124 (9.7)		
3: Moderate disability	23/126 (18.3)	13/124 (10.5)		
4: Moderately severe disability	11/126 (8.7)	12/124 (9.7)		
5: Severe disability	3/126 (2.4)	0/124		
6: Death	8/126 (6.3)	2/124 (1.6)		
Secondary end points				
Score on Markwalder Grading Scale at discharge — no./total no. (%)			Adjusted common odds ratio†	0.16 (0.09–0.30)
0 or 1	68/122 (55.7)	96/110 (87.3)		
2–4	49/122 (40.2)	14/110 (12.7)		
Death	5/122 (4.1)	0/110		
Score on modified Rankin scale at discharge — no./total no. (%)			Adjusted common odds ratio†	0.28 (0.16–0.50)
0–3	74/114 (64.9)	91/104 (87.5)		
4 or 5	35/114 (30.7)	13/104 (12.5)		
6	5/114 (4.4)	0/104		
Score on Markwalder Grading Scale at 2 wk — no./total no. (%)			Adjusted common odds ratio†	0.40 (0.23–0.69)
0 or 1	68/115 (59.1)	96/114 (84.2)		
2–4	43/115 (37.4)	16/114 (14.0)		
Death	4/115 (3.5)	2/114 (1.8)		
Score on modified Rankin scale at 2 wk — no./total no. (%)			Adjusted common odds ratio†	0.40 (0.23–0.68)
0–3	78/111 (70.3)	95/110 (86.4)		
4 or 5	29/111 (26.1)	13/110 (11.8)		
6	4/111 (3.6)	2/110 (1.8)		
Mean hematoma thickness at 2 wk — mm			Unadjusted beta	
Left side	15.7±6.4	11.9±5.1		3.80 (2.36–5.23)
Right side	17.1±6.8	12.5±5.8		4.60 (3.03–6.17)
Score on Markwalder Grading Scale at 3 mo — no./total no. (%)			Adjusted common odds ratio†	0.60 (0.34–1.05)
0: Neurologically intact	58/124 (46.8)	78/121 (64.5)		
1: Alert, oriented; mild symptoms such as headache	48/124 (38.7)	31/121 (25.6)		
2: Drowsy or disoriented with variable deficits	9/124 (7.3)	10/121 (8.3)		
3: Stuporous; responding to stimuli, severe focal signs	1/124 (0.8)	0/121		
4: Comatose with lack of motor responses	0/124	0/121		
Death	8/124 (6.5)	2/121 (1.7)		

Table 2. (Continued.)

Variable	Dexamethasone (N=127)	Surgery (N=125)	Measure of Effect	Difference or Odds Ratio (95% CI)
Score on Extended Glasgow Outcome Scale at 3 mo — no./total no. (%)‡			Adjusted common odds ratio†	0.67 (0.38–1.15)
1: Death	8/112 (7.1)	2/115 (1.7)		
2: Vegetative state	4/112 (3.6)	0/115		
3: Severe disability, lower	5/112 (4.5)	7/115 (6.1)		
4: Severe disability, upper	15/112 (13.4)	9/115 (7.8)		
5: Moderate disability, lower	6/112 (5.4)	3/115 (2.6)		
6: Moderate disability, upper	8/112 (7.1)	6/115 (5.2)		
7: Good recovery, lower	21/112 (18.8)	23/115 (20.0)		
8: Good recovery, upper	45/112 (40.2)	65/115 (56.5)		
Death — no. (%)	8 (6.3)	2 (1.6)	Adjusted odds ratio†	2.63 (0.43–16.67)
Recurrence due to failure of therapy — no. (%)				
Resulting in additional surgery	70 (55.1)	8 (6.4)	Unadjusted odds ratio	17.96 (8.09–39.85)
Resulting in additional therapy§	77 (60.6)	21 (16.8)	Unadjusted odds ratio	3.14 (1.93–5.12)
Total duration of hospital stay — days within 3 mo				
Median (range)	4 (0–43)	8 (0–57)		
Mean	12.0±10.6	6.8±6.7	Unadjusted beta	5.20 (3.00–7.40)

* Plus–minus values are means ±SD.
† Adjusted common odds ratios are for a better outcome with dexamethasone than with surgery, regardless of the direction of the scale (the Extended Glasgow Outcome Scale is in the opposite direction from the other scales with respect to severity). An adjusted odds ratio is used for the occurrence of death. Ratios were calculated with ordinal or logistic regression, with adjustment for age, sex, score on the Markwalder Grading Scale at diagnosis, score on the modified Rankin scale at baseline, history of stroke, history of atrial fibrillation, history of hypertension, history of acute myocardial ischemia, history of diabetes, and use of antithrombotic therapy.
‡ The Extended Glasgow Outcome Scale is an ordinal outcome scale assessing functional independence, work, social and leisure activities, and personal relationships. Its eight outcome categories are as follows: death, vegetative state (unable to obey commands), lower severe disability (dependent on others for care), upper severe disability (independent at home), lower moderate disability (independent at home and outside the home but with some physical or mental disability), upper moderate disability (independent at home and outside the home but with some physical or mental disability, with less disruption than lower moderate disability), lower good recovery (able to resume normal activities with some injury-related problems), and upper good recovery (no injury-related problems).
§ Additional therapy indicates surgery, the use of additional dexamethasone, or both.

patients had undergone randomization, of whom 127 were assigned to the dexamethasone group and 125 to the surgery group. The main reasons for nonenrollment are described in Figure 1. Two patients who were assigned to the dexamethasone group received initial surgical treatment because they declined dexamethasone, and 3 patients who were assigned to the surgery group initially received dexamethasone, primarily because they declined surgery. One patient in the dexamethasone group and 4 patients in the surgery group did not receive either trial treatment because their clinical condition improved, but they were included in the primary analysis. Two patients were lost to follow-up for the primary end point at 90 days and were excluded from the primary analysis.

In the total trial population, the mean (±SD) age was 74±11 years, and 195 of 252 patients (77.4%) were men. Data on race were not collected, and the representativeness of the trial population is shown in Table S4. Baseline characteristics were similar in the two trial groups (Table 1), except for the score on the modified Rankin scale at admission, with 48 of 127 patients (37.8%) in the dexamethasone group and 80 of 125 (64.0%) in the surgery group having a score of 0 to 3. A total of 190 of 252 patients (75.4%) across the trial had had known head trauma before the development of the chronic

Table 3. Adverse Events.

Event	Dexamethasone (N=127)	Surgery (N=125)
Adverse events		
No. of events	144	89
Mean no. per patient	1.13	0.71
Serious adverse events		
No. of events	102	65
Mean no. per patient	0.80	0.52
Patients with ≥1 complication — no. (%)	75 (59.1)	40 (32.0)
Subgroups of complications		
Infection — no. (%)	29 (22.8)	24 (19.2)
Empyema — no./total no. (%)	2/29 (7)	1/24 (4)
Gastrointestinal infection — no./total no. (%)	1/29 (3)	0/24
Wound infection — no./total no. (%)	0/29	1/24 (4)
Pneumonia — no./total no. (%)	8/29 (28)	2/24 (8)
Sepsis — no./total no. (%)	0/29	1/24 (4)
Thrombophlebitis — no./total no. (%)	0/29	1/24 (4)
Urinary tract infection — no./total no. (%)	10/29 (34)	9/24 (38)
Other — no./total no. (%)	8/29 (28)	9/24 (38)
Hyperglycemia — no. (%)	25 (19.7)	5 (4.0)
Delirium — no. (%)	20 (15.7)	7 (5.6)

subdural hematoma, and 142 of 252 patients (56.3%) had a history of antithrombotic medication use (77 of 127 in the dexamethasone group and 65 of 125 in the surgery group). Slightly more patients in the dexamethasone group than in the surgery group had a bilateral subdural hematoma: 43 of 127 (33.9%) and 33 of 125 (26.4%), respectively. Among patients assigned to the dexamethasone group, the median treatment duration was 19 days (interquartile range, 14.3 to 19.0), and 75 of 127 patients (59.1%) completed the full course of treatment. Patients who were assigned to the surgery group underwent burr-hole drainage a median of 2 days (interquartile range, 1.0 to 5.0) after randomization. Surgery was mostly performed with local anesthesia and the placement of a subdural or subgaleal drain (Table S3).

PRIMARY END POINT

The adjusted common odds ratio for a lower score on the modified Rankin scale at 3 months, indicating better outcomes with dexamethasone than with surgery, was 0.55 (95% confidence interval [CI], 0.34 to 0.90; P=0.02) (Table 2 and Fig. 2). Because the lower limit of the 95% confidence interval was not greater than or equal to the prespecified value of 0.9, noninferiority of dexamethasone was not established.

SECONDARY END POINTS

The adjusted common odds ratio for a lower score on the Markwalder Grading Scale at 3 months, indicating better outcomes with dexamethasone than with surgery, was 0.60 (95% CI, 0.34 to 1.05). The adjusted common odds ratio for a higher Extended Glasgow Outcome Scale score at 3 months, indicating better outcomes with dexamethasone than with surgery, was 0.67 (95% CI, 0.38 to 1.15). Functional outcomes at discharge and at 2 weeks as indicated by the scores on the Markwalder Grading Scale and the modified Rankin scale are shown in Table 2. Death at 3 months was reported in 8 of 127 patients (6.3%) in the dexamethasone group and 2 of 125 (1.6%) in the surgery group (adjusted odds ratio, 2.63; 95% CI, 0.43 to 16.67).

Overall, additional therapy after the index

treatment was received by 77 of 127 patients (60.6%) in the dexamethasone group and 21 of 125 patients (16.8%) in the surgery group. In the dexamethasone group, 70 of 127 patients (55.1%) underwent surgery at a median of 20 days (range, 1 to 127) after randomization; 35 of these procedures occurred before the 19-day planned course of dexamethasone was completed, and 7 of 127 patients (5.5%) received a second course of the drug (Table S3). In the surgery group, additional therapy consisted of repeat surgery in 8 of 125 patients (6.4%) and dexamethasone therapy in 13 of 125 patients (10.4%).

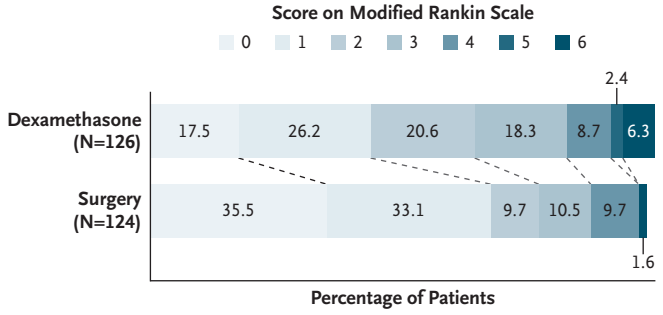

Figure 2. Scores on the Modified Rankin Scale at 3 Months.

A score of 0 indicates no symptoms, 1 no clinically significant disability despite symptoms, 2 slight disability, 3 moderate disability, 4 moderately severe disability, 5 severe disability, and 6 death. The common odds ratio for a better outcome with dexamethasone than with surgery was 0.55 (95% confidence interval, 0.34 to 0.90; P=0.02).

ADVERSE EVENTS

During 3 months of follow-up, 144 adverse events occurred in the dexamethasone group and 89 occurred in the surgery group; 102 and 65 serious adverse events occurred in the respective groups (Table 3). Infection was reported in 29 of 127 patients (22.8%) in the dexamethasone group and in 24 of 125 patients (19.2%) in the surgery group; hyperglycemia was reported in 25 patients (19.7%) and in 5 patients (4.0%), respectively; and delirium was reported in 20 patients (15.7%) and in 7 patients (5.6%). The mean (±SD) total length of hospital stay within 3 months was 12.0±10.6 days in the dexamethasone group and 6.8±6.7 days in the surgery group.

DISCUSSION

In this multicenter, open-label, randomized trial conducted in the Netherlands and involving patients with symptomatic chronic subdural hematoma, we investigated whether a 19-day tapering course of dexamethasone therapy would be noninferior to surgery by burr-hole drainage with respect to functional outcomes at 3 months. The trial was stopped early because of concerns about complications and poor outcomes with dexamethasone. From the available outcomes when the trial was stopped, we could not affirm the noninferiority of dexamethasone on the basis of a prespecified margin. The trial was not designed to test the superiority of either approach, but most results numerically favored surgery. With respect to secondary end points, results were heterogeneous at various time points but were generally in the same direction as those in the primary analysis. A total of 55% of the patients in the dexamethasone group eventually underwent surgery, as compared with 6% of those in the surgery group who underwent reoperation. More patients in the dexamethasone group than in the surgery group died, and patients in the dexamethasone group had more complications and longer hospital stays than those in the surgery group.

These findings are broadly in line with those of the recent Dexamethasone for Adult Patients with a Symptomatic Chronic Subdural Haematoma (Dex-CSDH) trial, in which dexamethasone therapy for chronic subdural hematoma also resulted in worse outcomes than placebo.[10] Whereas in the Dex-CSDH trial 94% of patients underwent surgery after randomization, in our trial we waited for the potential effect of dexamethasone as a monotherapy for a prespecified period of 2 weeks. Thereafter, the decision to initiate additional treatment for residual or recurrent hematoma, mostly surgery after dexamethasone, was made on the basis of clinical and imaging findings, provided that the patient's condition did not deteriorate (with deterioration defined as an increase of ≥1 point in the score on the Markwalder Grading Scale). This difference in trial design might explain the lower but still substantial incidence (55%) of surgery after dexamethasone therapy in our trial. In general agreement with the results of the Dex-CSDH trial, we observed more complications, including serious adverse events, in the dexamethasone group. The administration regimen for dexamethasone was similar in the two trials.

Although beneficial effects of dexamethasone for chronic subdural hematoma were reported in uncontrolled studies, those studies were limited by small numbers of patients and a lack of formal comparator groups.[9] Whether dexamethasone therapy has a potential role in selected cases or with specific imaging characteristics of chronic subdural hematoma or smaller hematomas is not addressed in our trial, but other investigations are ongoing.[14] Asymptomatic or severely affected patients with a score of 0 or 4, respectively, on the Markwalder Grading Scale were not eligible for inclusion in our trial.

Our trial has limitations. First, a large number of patients were screened, and approximately three fourths were not enrolled. The lack of treatment guidelines for chronic subdural hematoma and differences in local practices may have influenced the decisions of surgeons at participating centers not to enroll patients in the trial. However, the baseline characteristics and inclusion rate observed in our trial were similar to those of other studies.[6,10] Second, the timing and decision to perform surgery after initial dexamethasone therapy could have been influenced by the open-label design and local practice, despite the criteria in the protocol. Third, most patients enrolled in this trial had scores on the Markwalder Grading scale of 1 or 2 (not 3, which signifies a severe focal neurologic deficit). Therefore, conclusions from this trial apply mainly to patients who are alert or drowsy with slight-to-moderate focal neurologic deficits. Fourth, by chance, the level of functional impairment at admission was higher in the dexamethasone group than in the surgery group, which could have disadvantaged the outcomes for the former group. However, the primary analysis was adjusted for the scores on the modified Rankin scale and the Markwalder Grading Scale at admission.

In this multicenter, randomized trial involving symptomatic patients with chronic subdural hematoma, dexamethasone therapy was not found to be noninferior to surgery by burr-hole drainage. Patients who received dexamethasone more frequently underwent additional surgery and had more adverse events than patients who initially had surgical drainage.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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

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