Chronic subdural hematoma: tailoring treatment

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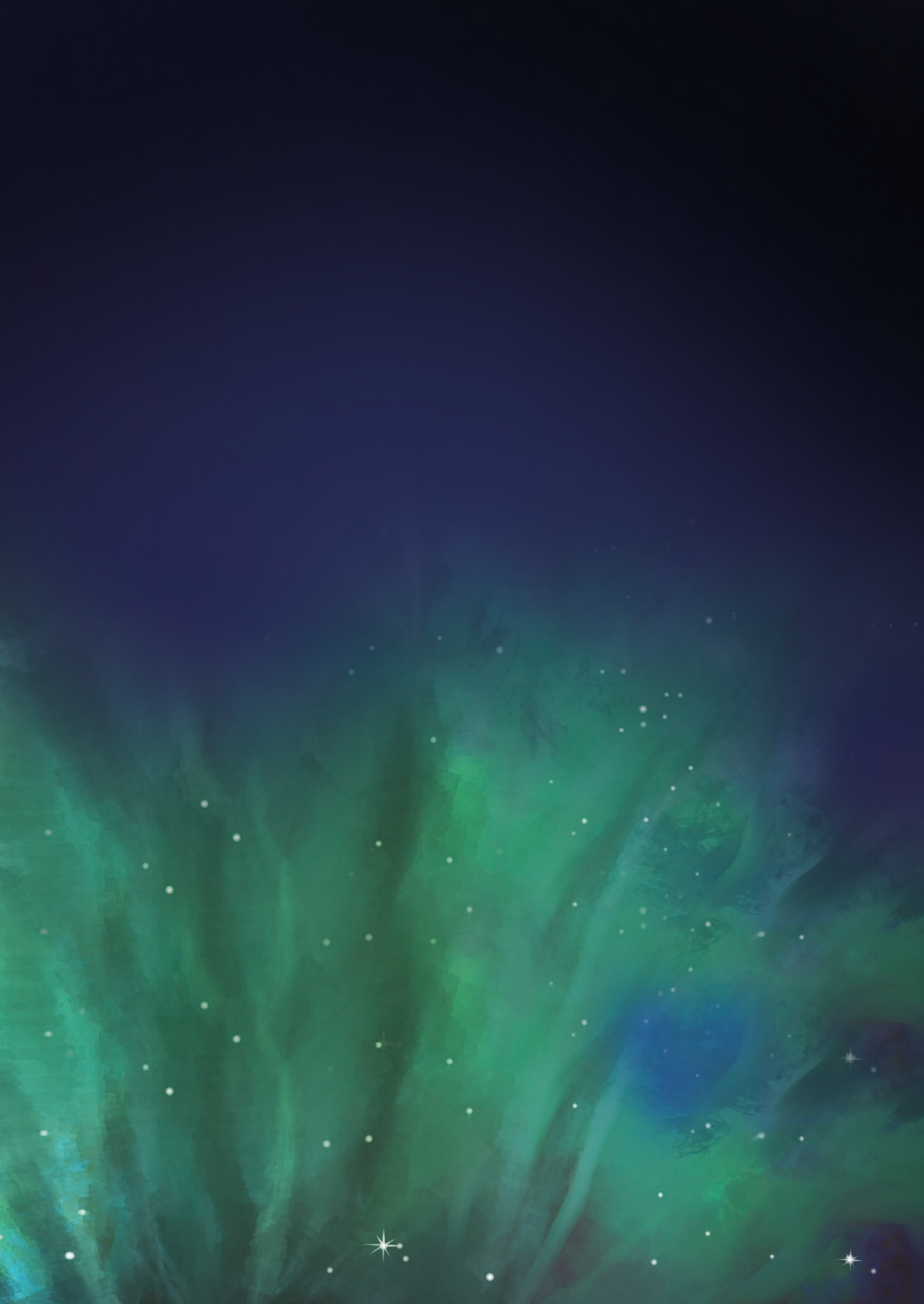

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Dexamethasone therapy versus surgery for symptomatic patients with chronic subdural hematoma (DECSA – trial)

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Abstract

Background

The optimal treatment for symptomatic chronic subdural hematoma is unclear. We aimed to assess the effectiveness of dexamethasone therapy compared with surgical evacuation in patients with symptomatic chronic subdural hematoma in a multicenter, randomized controlled trial.

Methods

Symptomatic patients with a chronic subdural hematoma, defined as Markwalder Grading Scale score 1 to 3, were eligible for the study. We randomly assigned patients in a 1:1 ratio to a 19-day oral dexamethasone tapering course or surgical evacuation through burr-hole craniostomy. The primary outcome was functional outcome as expressed by the modified Rankin Scale (ranging from 0 (no symptoms) to 6 (death)), at three months after randomization, analyzed with an adjusted proportional odds regression (aOR). Secondary endpoints included Markwalder Grading Scale (MGS) and Glasgow Outcome Scale-Extended (GOSE) scores, additional treatment, complications and mortality within three months.

Results

From September 2016 through February 2021, we enrolled 252 patients; 127 were assigned to dexamethasone therapy and 125 to surgery. Mean age was 74 years (Standard Deviation [SD] 11) and 77% were male. Markwalder grading scale scores were 1, 2 and 3 in 38%, 61% and 1% of patients respectively. A favorable modified Rankin Scale score (0-3) at three months was achieved in 82% in the dexamethasone group versus 89% in the surgery group. The aOR for a higher (i.e. worse) modified Rankin Scale score at three months for dexamethasone compared to surgery was 2.28 (95% confidence interval [CI], 1.43 to 3.64). The dexamethasone group also had worse scores on the Glasgow Outcome Scale – Extended (aOR of 0.67 for a higher score, 95% CI, 0.38 to 1.15) and MGS (aOR of 1.67 for a higher Markwalder Grading Scale score, 95% CI, 0.95 to 2.94) at three months. Additional therapy (61% vs. 17%), complications (136 versus 66) and mortality (6.3% vs. 1.6%) occurred more often in the dexamethasone group.

Conclusions

Surgery for symptomatic chronic subdural hematoma compared with dexamethasone therapy results in a significantly better functional outcome and less complications. (Funded by the Netherlands Organization for Health Research and Development; EudraCT: 2015-001563-39.)

Introduction

Chronic subdural hematoma is a frequent neurologic disorder and associated with a rising prevalence due to increasing age and widespread use of antithrombotics [1-2]. A minor head trauma often initiates the hematoma development followed by a subsequent inflammatory response in the newly formed subdural space [3-4], which leads to a broad variety of clinical symptoms [5].

Surgical hematoma evacuation through burr-hole craniostomy combined with subdural drainage is the mainstay treatment in symptomatic patients worldwide [6]. Albeit very effective, this treatment is associated with complications, mortality and recurrence rates up to 30%, despite the optimization of surgical techniques [7]. In addition, the presence of comorbidities can complicate surgical treatment, especially in high-risk patients. Oral dexamethasone therapy has been proposed as an alternative, non-operative treatment. Dexamethasone has the potential to block the inflammatory changes in the subdural space, impeding hematoma persistence and growth, and is therefore administered routinely in various institutions [8].

Although earlier studies and systematic reviews have shown that glucocorticosteroids as dexamethasone are safe and effective as therapy for chronic subdural hematoma, a recent large randomized trial found dexamethasone to result in fewer favorable outcomes and more adverse events [9]. In this trial, however, most patients had undergone surgical evacuation during the index admission. Whether dexamethasone monotherapy has an equal potential to surgery to achieve favorable outcomes in patients with a chronic subdural hematoma remains unclear.

We conducted a multicenter, randomized controlled non-inferiority trial to compare dexamethasone treatment as stand-alone therapy with 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 study design [10]. The trial was conducted in 12 hospitals in The Netherlands (table S1 in the Supplementary Appendix). A DECSA-research group was established to gather coordinating and local investigators. The trial compared a 19-day oral dexamethasone tapering course with surgical evacuation through burr-hole craniostomy in patients with symptomatic chronic subdural hematoma. The study hypothesis was that dexamethasone was non-inferior to surgery with respect to the functional outcome at three months. Details of the protocol have been published previously and the study protocol is available with the full text of this article [11].

For participation, written informed consent was obtained from the patients or from their legal representative if they lacked the capacity to provide consent. The coordinating investigators physically or virtually visited study centers every three months on-site to discuss any issues and check on conduct of the study. The trial steering committee assembled every six weeks to discuss conduct, progress, and safety of the trial. Case Record Form data were monitored yearly by independent external experts throughout the study to verify adherence to the protocol and data completeness, consistency and accuracy. An independent Data Safety Monitoring Board (DSMB) reviewed the trial according to a dedicated charter for study safety and efficacy. Prespecified interim analyses of major endpoints, including all serious adverse events during the study period, were planned after inclusion of 150 and 300 patients. A prespecified interim analysis of data was performed after 150 patients had completed the period of three months follow-up for the primary outcome measure in order to ensure study safety and efficacy. After this planned analysis the data and safety monitoring board requested an unplanned additional review of the actual number of included patients. This analysis resulted in premature termination of the trial since the outcomes were substantially worse in the dexamethasone group and complication rates were overtly unbalanced in the disadvantage of dexamethasone therapy. In this manuscript we report the analysis of the primary and secondary outcomes within three months follow-up.

The investigators vouch for the completeness and accuracy of the data, for the complete reporting of adverse events, for the adherence of the trial to the protocol and for the statistical analysis. The first draft of the manuscript was written by the two first authors and the three last authors and was revised by all authors, who collectively agreed to submit the manuscript for publication. The trial was funded by the non-profit organizations Stichting Jacobus The Hague, Netherlands Organization for Health Research and Development (ZonMw) and Erasmus Medical Center (Mrace). The sponsors had no involvement in the study design, study conduct, protocol review, or manuscript preparation or review.

Patients

We recruited patients aged 18 years or older from the outpatient clinic and emergency department with a newly diagnosed symptomatic chronic subdural hematoma on computed tomography (CT) scan, defined as a predominantly hypodense or iso-dense collection of fluid (relative to brain parenchyma) in the subdural space. For inclusion, clinical symptoms had to be attributable to the chronic subdural hematoma and had a Markwalder Grading Scale score between 1 (only headache) to 3 (severe focal neurological deficit). The Markwalder Grading Scale is a validated grading system (scores ranging 0–4; 0 is asymptomatic and 4 is coma with absent motor responses to painful stimuli) to classify the neurological condition for chronic subdural hematoma patients [12]. Patients with an acute hematoma defined as a predominantly hyperdense subdural collection on CT were not eligible for randomization. Other exclusion criteria were asymptomatic or comatose patients. a poorly regulated diabetes mellitus defined as HbA1c value >8% (64 mmol.mol-1), glaucoma, pregnancy, presence of a cerebrospinal fluid shunt, and conditions for which glucocorticoids are contraindicated such as hypersensitivity to dexamethasone, actual or recent ulcerations or bleeding in the gastrointestinal tract, an acute systemic infection, or a history of psychotic disorders.

Trial procedures

Patients were randomly assigned in a 1:1 allocation ratio stratified for study site to either the dexamethasone or the surgical group. Balanced random samples were generated through stratified block-randomization using a computer randomization algorithm. For all included patients, antithrombotic therapies were halted on the day of randomization.

Dexamethasone therapy was administered orally in tablets, or intravenously when oral administration was not possible, in a 19-days tapering course (8 mg

every 12 hours on day 1 to 4, tapered by half every 3 days until a dosage of 0.5 mg a day on day 19 and stopped on day 20, comprising a total of 110.5 mg dexamethasone). The treatment could be completed at home if patients were discharged. For patients assigned to surgery, the treatment was scheduled within seven days after randomization to provide a safe interval in case of antithrombotic therapy use. At the discretion of the surgeon, earlier intervention was allowed if deemed clinically necessary. In all participating hospitals the standard neurosurgical practice to treat chronic subdural hematoma was burr-hole evacuation of the hematoma followed by insertion of a subdural drain for two days. Preoperative antibiotic prophylaxis was administered and either general or local anesthesia could be applied according to local practice. All patients underwent a follow-up CT at two weeks after initiation of treatment.

Discontinuation of dexamethasone therapy was indicated in case of failure to improve within two weeks of treatment, defined as an unchanged Markwalder Grading scale score, or evidence of an increase in hematoma size on follow-up CT. Other reasons to discontinue dexamethasone therapy were clinical deterioration at any time after initiation of treatment, defined by ≥1 point increase in Markwalder Grading scale score, or the occurrence of severe, dexamethasone related side effects or complications. Whenever dexamethasone was discontinued, additional surgical treatment could be applied to treat the remaining symptoms. Reoperation after initial surgical treatment was indicated when neurological deficits did not resolve, deteriorated or recurred within the follow-up period, and CT demonstrated residual or recurrent hematoma.

Outcomes

The primary endpoint was the functional outcome expressed by the modified Rankin Scale at three months after randomization. The modified Rankin Scale is an ordinal outcome scale of disability or dependence, and is nowadays frequently used to assess neurological or neurosurgical outcome. The scale consists of 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) [13].

At the coordinating trial centers trained physicians and research nurses assessed modified Rankin Scale scores according to a standardized algorithm. Patients were evaluated at baseline and discharge from the hospital, and at two weeks and three months after randomization. The research nurse performed

the three months functional outcome evaluation by phone and was unaware of trial-group assignment.

Secondary outcomes the modified Rankin Scale score at discharge and two weeks; the Markwalder Grading Scale score at discharge, two weeks and three months; the Glasgow Outcome Scale – Extended, which is an eight-point scale, varying from dead (score 1) to upper good recovery (score 8) at three months; symptomatic residual or recurrent hematoma on follow-up CT requiring additional intervention within three months after index treatment; number of additional interventions; overall complications including surgical and drug-related adverse events with special interest in hyperglycemia, infection and mood disorders; overall length of hospital stay within three months and mortality at three months.

Power calculation

We hypothesized that dexamethasone therapy for chronic subdural hematoma would be non-inferior to surgery on functional outcome as expressed by modified Rankin Scale score at three months. In assuming that the true effect of dexamethasone has an odds ratio of 1.15 for a better functional outcome on the modified Rankin Scale, we aimed to include 420 patients to attain a power of 90%. To accept the null hypothesis of non-inferiority the lower 95% confidence limit of the odds ratio for a better functional outcome of dexamethasone compared to surgery had to be equal to or above 0.9.

Statistical analysis

The analysis was conducted according to a statistical analysis plan. The primary analysis consisted of estimating the adjusted common odds ratio for a shift in the direction of a better outcome on the modified Rankin Scale at three months for all randomized patients in the two treatment groups. The odds ratio was estimated on an intention-to-treat basis with a multivariable proportional odds logistic regression with adjustment for the covariates pre-specified in the protocol. Patients with missing outcomes were excluded. For secondary outcome measures, ordinal outcomes were analyzed with proportional odds logistic regression and binary outcomes with binary logistic regression. As a sensitivity analysis we describe the primary outcome measure in a per-protocol fashion, defined as patients in the intention-to-treat population receiving treatment as randomized without protocol violation. Given the smaller sample size than originally anticipated, we did not perform any subgroup analysis. A

p-value of less than 0.05 indicated statistical significance. For all analyses, we used R statistical software.

Results

Between September 2016 and February 2021, 1039 patients were screened for study participation at 12 Dutch hospitals. In total, 252 patients were randomized of whom 127 patients to dexamethasone therapy and 125 to surgery by burr-hole craniostomy (figure 1). Two patients randomized in the dexamethasone group received surgical treatment because they refused treatment with dexamethasone, three patients in the surgery group received dexamethasone as primary treatment after randomization because they rejected surgery. One patient in the dexamethasone group and four patients in the surgery group did not undergo any treatment because clinical condition improved. Four patients were lost to follow-up for the primary outcome.

In the total study population, mean age was 74 years (SD 11) and 77.4% were male. Baseline characteristics were well-balanced (table 1) except from premorbid modified Rankin Scale score with 82.7% of the patients in the dexamethasone group having a score of 0 to 2 versus 90.3% in the surgery group. Approximately 75% of patients in both groups had an evident head trauma preceding the development of the chronic subdural hematoma, and over half of the patients (56.3%) had a history of antithrombotic medication use. Slightly more patients in the dexamethasone group had a bilateral subdural hematoma, 33.9% versus 26.4%. For the patients randomized to dexamethasone therapy the median treatment duration was 19 days (interquartile range [IQR] 14.3-19.0) and 59.1% of patients completed the full course of dexamethasone treatment. Patients randomized to surgery underwent burr-hole craniostomy after a median of two days (IQR 1.0-5.0). Surgery was mostly performed by performing one burr-hole under local anesthesia with application of a subdural or subgaleal drain (table S2 in the Supplementary Appendix).

Primary outcome

Patients who had missing primary outcome were excluded from the primary analysis. Fewer patients in the dexamethasone group had a favorable functional outcome at three months than in the surgery group (table 2); 102 of 124 patients (82.3%) and 110 of 124 (88.7%) respectively. The acOR for a worse functional outcome associated with dexamethasone therapy at three months was 2.28

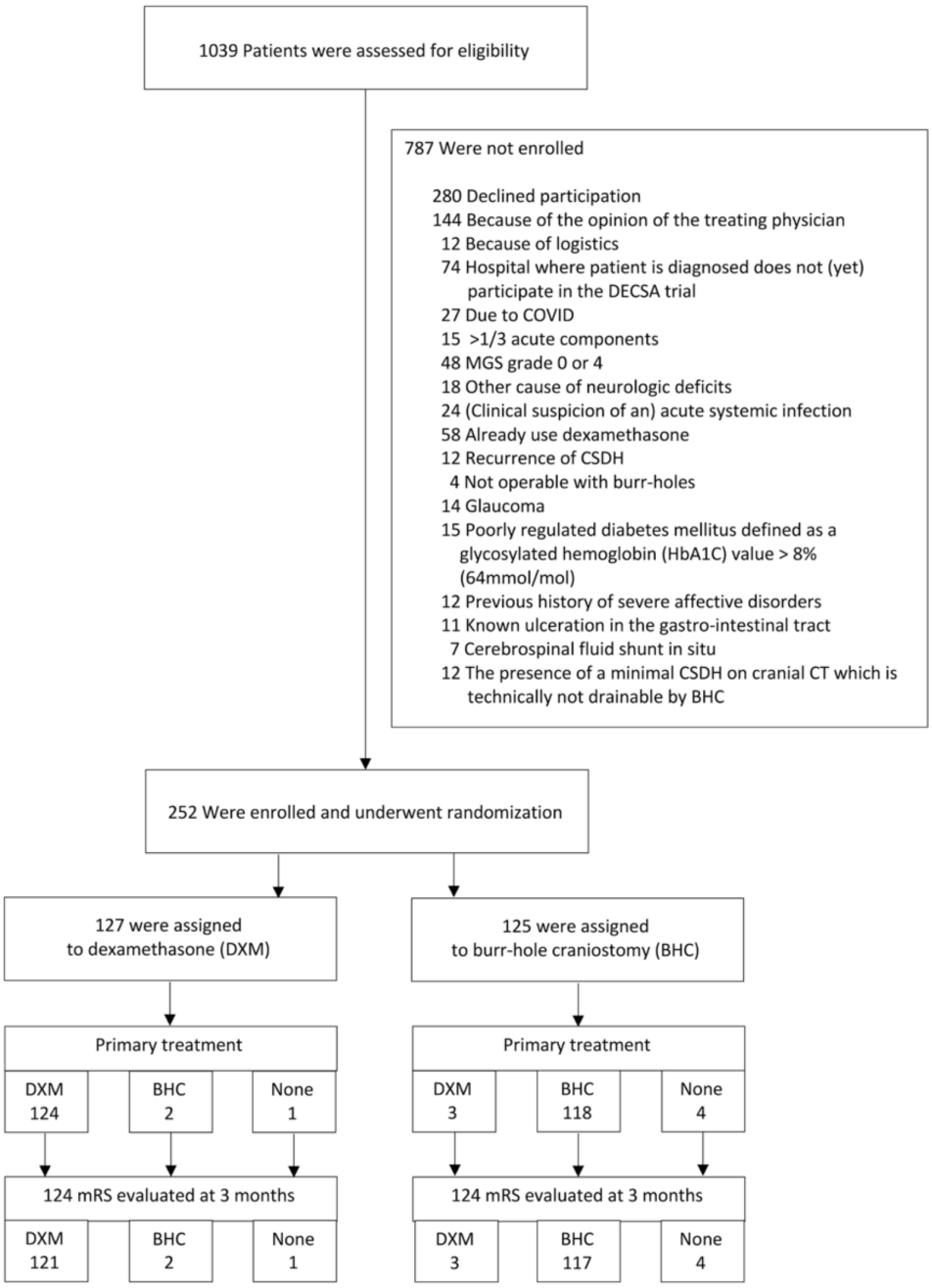

Figure 1. Flowchart of randomized patients, their primary treatment and follow-up status.

Table 1. Characteristics of the patients at baseline.

Characteristic	Dexamethasone (N =127)	Surgery (N=125)
Age – year	75.4 ± 10.2	73.5 ± 11.1
Male sex – no./total no. (%)	99/127 (78.0)	96/125 (76.8)
Symptoms at presentation – no./total no. (%)		
Headache	65/127 (51.2)	66/125 (52.8)
Gait disturbance	89/127 (70.1)	74/125 (59.2)
Altered mental status	81/127 (63.8)	62/125 (49.6)
Hemiparesis	86/127 (67.7)	61/125 (48.8)
Speech disorder	41/127 (32.3)	29/125 (23.2)
Seizure(s)	9/127 (7.1)	2/125 (1.6)
Nausea and vomiting	13/127 (10.2)	14/125 (11.2)
Other	58/127 (45.7)	44/125 (35.2)
Premorbid modified Rankin Scale score – no./total no. (%)		
0: No symptoms	67/127 (52.8)	90/125 (72.0)
1: No clinically significant disability	25/127 (19.7)	12/125 (9.6)
2: Slight disability	13/127 (10.2)	10/125 (8.0)
3: Moderate disability	13/127 (10.2)	7/125 (5.6)
4: Moderately severe disability	9/127 (7.1)	5/125 (4.0)
5: Severe disability	0/127 (0.0)	1/125 (0.8)
Markwalder Grading Scale score at admission – no./total no. (%)		
1: Alert, oriented. Mild symptoms such as headache.	33/127 (26.0)	59/125 (47.2)
2: Drowsy or disoriented with variable deficits.	93/127 (73.2)	65/125 (52.0)
3: Stuporous; responding to stimuli, severe focal signs.	1/127 (0.8)	1/125 (0.8)
1: Alert, oriented. Mild symptoms such as headache.	33/127 (26.0)	59/125 (47.2)
2: Drowsy or disoriented with variable deficits.	93/127 (73.2)	65/125 (52.0)
3: Stuporous; responding to stimuli, severe focal signs.	1/127 (0.8)	1/125 (0.8)
modified Rankin Scale score at admission – no./total no. (%)		
1-3	48/127 (37.8)	80/125 (64.0)
4-5	79/127 (62.2)	45/125 (36.0)
Known head trauma – no./total no. (%)	95/127 (74.8)	95/125 (76.0)
Main coexisting medical conditions – no./total no. (%)		
None	7/127 (5.5)	7/125 (5.6)
Atrial fibrillation	30/127 (23.6)	24/125 (19.2)
Diabetes	22/127 (17.3)	24/125 (19.2)
Ischemic heart disease	28/127 (22.0)	12/125 (9.6)
Previous stroke	23/127 (18.1)	24/125 (19.2)
Any antithrombotic medication – no./total no. (%)	77/127 (60.6)	65/125 (52.0)
Bilateral CSDH on CT scan – no./total no. (%)	43/127 (33.9)	33/125 (26.4)
Midline shift in unilateral CSDH on admission CT scan in mm	9.2 ± 3.9	9.0 ± 3.8
no./total no. (%)	84/127 (66.1)	92/125 (73.6)
0-5 mm	13/84 (15.5)	14/92 (15.2)
6-10 mm	34/84 (40.5)	42/92 (45.7)
>10 mm	37/84 (44.0)	36/92 (39.1)

(95% CI, 1.43 to 3.64) indicating worse outcomes in the dexamethasone group. (Table 2; figure 2).

Secondary outcomes

A good clinical outcome, expressed with the Markwalder Grading Scale score at three months, defined as a score of 0, was observed in 58 of 124 (46.8%) patients in the dexamethasone group, compared with 78 of 121 (64.5%) patients in the surgical group. The acOR for a higher Markwalder Grading Scale score was 1.67 (95% CI, 0.95 to 2.94), again indicating worse outcomes in the dexamethasone group. A good functional recovery expressed by a score of 7 to 8 on the Glasgow Outcome Scale – Extended at three months, was reported in 66 of 112 (58.9%) patients in the dexamethasone group versus 88 of 115 (76.5%) patients in the surgical group. The acOR for a higher Glasgow Outcome Scale – Extended score was 0.67 (95% CI 0.38 to 1.15) again indicating worse outcomes in the dexamethasone arm. Functional outcomes at discharge and two weeks showed similar results (table 2). Mortality at three months was reported in 8 of 127 (6.3%) in the dexamethasone group versus 2 of 125 (1.6%) in the surgical group with an aOR of 2.63 (95% CI 0.42 to 16.67).

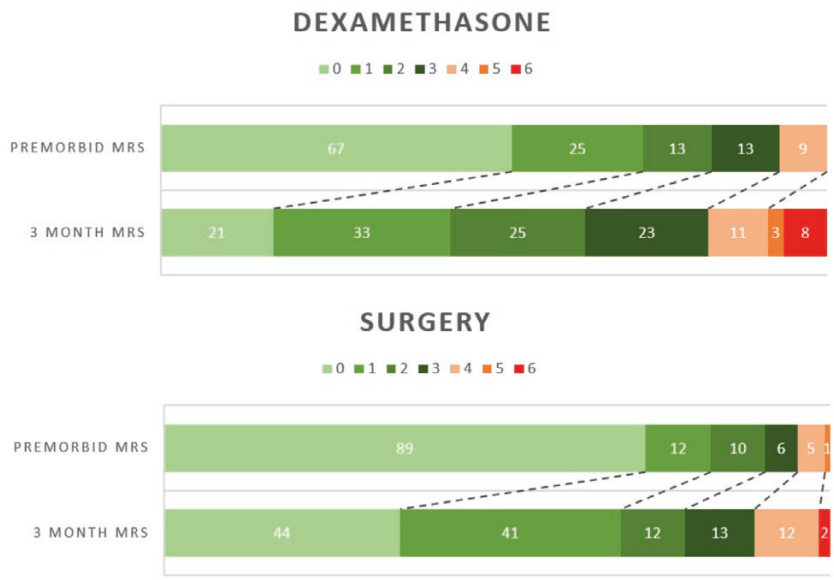

Figure 2. modified Rankin Scale. Comparison between dexamethasone and surgery in the premorbid phase and at 3 months

Table 2. Results

Variable	Dexamethasone	Surgery	Difference or Odds or Rate Ratio (95% CI)
Primary outcome			
Ordinal modified Rankin Scale score at 3 months – no./total no. (%)			2.28 (1.43-3.64)¶
0: No symptoms	21/124 (16.9)	44/124 (35.5)	
1: No clinically significant disability	33/124 (26.6)	41/124 (33.1)	
2: Slight disability	25/124 (20.2)	12/124 (9.7)	
3: Moderate disability	23/124 (18.5)	13/124 (10.5)	
4: Moderately severe disability	11/124 (8.9)	12/124 (9.7)	
5: Severe disability	3/124 (2.4)	0/124 (0.0)	
6: Dead	8/124 (6.5)	2/124 (1.6)	
Secondary outcomes			
Markwalder Grading Scale at discharge – no./total no. (%)			6.25 (3.33-11.11)¶
0-1	68/122 (55.7)	96/110 (87.3)	
2-4	49/122 (40.2)	14/110 (12.7)	
5	5/122 (4.1)	0/110 (0.0)	
modified Rankin Scale score at discharge – no./total no. (%)			3.57 (2.00-6.25)¶
0-2	40/114 (35.1)	76/104 (73.1)	
3-5	69/114 (60.5)	28/104 (26.9)	
6	5/114 (4.4)	0/104 (0.0)	
Markwalder Grading Scale at 2 weeks – no./total no. (%)			2.50 (1.45-4.35)¶
0-1	68/115 (59.1)	96/114 (84.2)	
2-4	43/115 (37.4)	16/114 (14.0)	
5	4/115 (3.5)	2/114 (1.8)	
modified Rankin Scale score at 2 weeks – no./total no. (%)			2.50 (1.47-4.35)¶
0-2	52/111 (46.8)	86/110 (78.2)	
3-5	55/111 (49.5)	22/110 (20.0)	
6	4/111 (3.6)	2/110 (1.8)	
Markwalder Grading Scale at 3 months – no./total no. (%)			1.67 (0.95–2.94)¶
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 (0.0)	
4: Comatose with absent motor responses	0/124 (0.0)	0/121 (0.0)	
5: Death	8/124 (6.5)	2/121 (1.7)	

Table 2. *continued*

Variable	Dexamethasone	Surgery	Difference or Odds or Rate Ratio (95% CI)
Glasgow Outcome Scale-Extended score at 3 months – no./total no. (%)			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 (0.0)	
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)	
Mortality – no./total no. (%)	8/127 (6.3)	2/125 (1.6)	2.63 (0.43-16.67)§
Additional surgery - no./total no. (%)	71/127 (55.9)	8/125 (6.4)	
Additional therapy - no./total no. (%)	77/127 (60.6)	21/125 (16.8)	2.86 (1.27-6.25)§

¶: Adjusted* common odds ratio; §: Adjusted* odds ratio. *ordinal regression analyses were performed for a higher score with surgery as reference treatment, adjusting for for age, sex and pre-morbid Modified Rankin Scale.

Additional surgery for symptomatic residual or recurrent hematoma was required in 71 of 127 (55.9%) patients in the dexamethasone group; repeat surgery was performed in 8 of 125 (6.4%) patients in the surgery group. Overall, additional therapy after the index treatment was applied in 77 of 127 (60.6%) in the dexamethasone group versus 21 of 125 (16.8%) patients in the surgical group (table 2).

A total of 144 adverse events occurred during three months follow-up in the dexamethasone group and a total of 89 in the surgery group and 102 and 65 serious adverse events occurred in the respective arms (table 3). The risk of any infection was 22.8% in the dexamethasone group and 19.2% in the surgery group, for hyperglycemia 19.7% and 4.0%, and for delirium 15.7% and 5.6%. The mean total length of hospital stay within 3 months was 12.0 days (SD 10.6) in the dexamethasone group and 6.8 (SD 6.7) in the surgery group.

In the per-protocol analysis, a favorable outcome at three months was achieved in 101 of 124 (81.5%) patients in the dexamethasone group and 106 of 119 (89.1%) patients in the surgical group (table S3 in the Supplementary Appendix).

Table 3. (Serious) adverse events

Variable	Dexamethasone	Surgery
Adverse events - no./total no. (mean no. per patient)	144/127 (1.13)	89/125 (0.71)
Serious adverse events - no./total no. (mean no. per patient)	102/127 (0.80)	65/125 (0.52)
Complications up to 3 months – total no.	136	66
Infection (total no.)	29/127 (22.8)	24/125 (19.2)
Empyema	2/29 (6.9)	1/24 (4.2)
Gastrointestinal infection	1/29 (3.4)	0/24 (0.0)
Wound infection	0/29 (0.0)	1/24 (4.2)
Pneumonia	8/29 (27.6)	2/24 (8.3)
Sepsis	0/29 (0.0)	1/24 (4.2)
Thrombophlebitis	0/29 (0.0)	1/24 (4.2)
Urinary tract infection	10/29 (34.5)	9/24 (37.5)
Infection other	8/29 (27.6)	9/24 (37.5)
Hyperglycaemia	25/127 (19.7)	5/125 (4.0)
Delirium	20/127 (15.7)	7/125 (5.6)
Total duration of hospital stay – days		
Median (min-max)	4 (0-43)	8 (0-57)
Mean ± standard deviation	12.0 ± 10.6	6.8 ± 6.7

Discussion

In this multicenter, randomized trial we investigated whether a 19-days tapering course of dexamethasone therapy for symptomatic chronic subdural hematoma, defined as a Markwalder Grading scale score of 1 to 3, was non-inferior to surgery by burr-hole craniostomy with respect to functional outcome at three months. We found that patients who were treated with dexamethasone had a significantly worse functional outcome compared to surgical treatment. Furthermore, additional surgery was required in 61% of patients treated with dexamethasone. Patients on dexamethasone therapy also had a higher mortality rate, significantly more complications, and a doubled length of hospital stay compared to surgery.

Contrary to our hypothesis, we found a worse functional outcome in the dexamethasone group compared with the surgical group necessitating the trial to end prematurely after the interim analysis. These findings are in line with the recent DEX-CSDH trial published in this Journal, in which dexamethasone therapy for chronic subdural hematoma compared to placebo also resulted in worse outcome [9]. Whereas in the DEX-CSDH trial overall 94% of the

patients underwent surgery after randomization, in our study we awaited the effect of dexamethasone therapy as a monotherapy for symptomatic chronic subdural hematoma the first two weeks. Thereafter, the decision to initiate additional treatment for residual or recurrent hematoma, mostly surgery after dexamethasone, was taken on clinical and radiological arguments, provided the patient did not deteriorate in the meantime. This different study design might explain the lower but still substantial rate of 61% additional surgery following dexamethasone therapy in our study.

In accordance to the results of the DEX-CSDH trial [9], we also observed significantly more complications, including serious adverse events, in the dexamethasone group. The dexamethasone dosing scheme was quite similar in both trials. It is possible that the high dosing scheme of dexamethasone contributed to the high complication rate. However, we have also observed significantly more complications in the dexamethasone arm after a lower and shorter dosing scheme of 6 to 8 mg a day during six days in the DECSA-R cohort study [14]. Moreover, lowering the dexamethasone dose would probably result in less therapeutic effect and subsequently a higher cross-over rate to surgery. Increasing the dexamethasone dose is expected to result in more (serious) adverse events, as was also revealed in a previous small pilot randomized trial applying dexamethasone 12 mg per day during three weeks [15].

Although beneficial effects of dexamethasone for chronic subdural hematoma have been shown in earlier non-randomized studies, these studies are limited by small patient numbers and imperfect methodological design [8]. Whether dexamethasone therapy has a potential role in selected cases in specific radiological hematoma subtypes or smaller hematomas is presently unknown [16]. Asymptomatic or severely affected patients with a Markwalder Grading Scale score of 0 and 4 respectively were not eligible for inclusion and were beyond the scope of the DECSA trial.

Our trial has limitations. First, a considerably larger number of patients was screened for study participation, but only a proportion was randomized. This could have compromised the reflection of real-life clinical practice; however, the baseline characteristics and inclusion rate are perfectly in line with other studies limiting this possibility [9, 17]. Second, the timing and decision to opt for additional surgery after initial dexamethasone therapy could have been influenced by local practice, despite protocolized criteria. An analysis demonstrated that the rate of performing additional surgery after

dexamethasone therapy was within close range for all neurosurgical centers. Third, due to premature halting of the study according to the advice of the DSMB after the results of the interim-analysis, demonstration of non-inferiority of dexamethasone and the analysis of subgroups was deemed unfeasible.

In this multicenter randomized trial involving symptomatic patients with a chronic subdural hematoma initial dexamethasone therapy resulted in worse functional outcome at three months compared to surgery by burr-hole craniostomy. Furthermore, patients treated with dexamethasone frequently required additional surgery had higher mortality, more adverse events, and longer length of stay. The results show there is no indication for dexamethasone therapy for patients with a symptomatic chronic subdural hematoma.

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