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Surgery After Primary Dexamethasone Treatment for Patients with Chronic Subdural Hematoma—A Retrospective Study

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■ BACKGROUND: **We aimed to quantify the need for additional surgery in patients with chronic subdural hematoma (CSDH) primarily treated with dexamethasone and to identify patient characteristics associated with additional surgery.**

■ METHODS: **Data were retrospectively collected from 283 patients with CSDH, primarily treated with dexamethasone, in 3 hospitals from 2008 to 2018. Primary outcome was the need for additional surgery. The association between baseline characteristics and additional surgery was analyzed with univariable and multivariable logistic regression analysis and presented as adjusted odds ratios (aOR).**

■ RESULTS: **In total, 283 patients with CSDH were included: 146 patients (51.6%) received 1 dexamethasone course (DXM group), 30 patients (10.6%) received 2 dexamethasone courses (DXM-DXM group), and 107 patients (37.8%) received additional surgery (DXM-SURG group). Patients who underwent surgery more often had a Markwalder Grading Scale of 2 (as compared with 1, aOR 2.05; 95% confidence interval [CI] 0.90—4.65), used statins (aOR 2.09; 95% CI 1.01—4.33), had a larger midline shift (aOR 1.10 per mm; 95% CI 1.01—1.21) and had larger hematoma thickness (aOR 1.16 per mm; 95% CI 1.09—1.23), had a bilateral hematoma (aOR 1.85; 95% CI 0.90—3.79), and had a separated hematoma (as compared with homogeneous, aOR 1.77; 95% CI 0.72—4.38). Antithrombotics (aOR 0.45; 95% CI 0.21—0.95) and trabecular hematoma (as compared with homogeneous, aOR 0.31; 95% CI 0.12—0.77) were associated with a lower likelihood of surgery.**

■ CONCLUSIONS: **More than one-third of patients with CSDH primarily treated with dexamethasone received additional surgery. These patients were more severely affected amongst others with larger hematomas.**

INTRODUCTION

Chronic subdural hematoma (CSDH) is commonly seen in neurologic and neurosurgical practice, with an overall increasing incidence of 1.72—79.6 per 100,000 persons per year.[1-6] Despite this increasing incidence, there is no consensus on the optimal treatment. This leads to a broad variation in CSDH management; not only internationally, but also on a

Key words
- CSDH
- Dexamethasone
- Medical
- Nonsurgical
- Treatment

Abbreviations and Acronyms
aOR: adjusted odds ratio
CI: Confidence interval
CSDH: Chronic subdural hematoma
CT: Computed tomography
DXM: Dexamethasone
MGS: Markwalder Grading Scale
SD: Standard deviation
SURG: Surgery

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national, regional, and hospital level.[7] Worldwide, burr-hole craniostomy is the most commonly performed intervention in symptomatic CSDH and is considered the gold standard.[8-12] The mechanism of CSDH formation relies on a complex intertwined pathway of angiogenesis, inflammation, recurrent microbleeds, exudates, and local coagulopathy.[13] The process of inflammation has led to consideration and implementation of other treatment options, such as corticosteroids as monotherapy or as an adjunct to surgery.[14] Conservative management and the use of corticosteroids in the treatment were initiated and extensively described by Dr. Bender, a neurologist at the Mount Sinai Hospital in New York.[15] Several observational studies suggest that steroids can be useful as both primary conservative therapy and as an adjunct to surgery to reduce CSDH recurrence.[15-25]

However, the recently published Dex-CSDH randomized controlled trial, including 748 patients with symptomatic CSDH, showed that a 2-week tapering course of dexamethasone compared with placebo resulted in a less-favorable outcome at 6 months.[26] According to standard clinical practice, the vast majority of these patients underwent surgery for hematoma evacuation. Therefore, no firm conclusions could be drawn regarding the effect of dexamethasone as a method of treatment to avoid surgery.

Over the years, the use of dexamethasone as a primary CSDH treatment option was gradually implemented in the region of Rotterdam. In 2011, the use of dexamethasone as a primary treatment was eventually adopted in the regional CSDH guidelines. According to this guideline, surgery is indicated if clinical deterioration takes place or when no improvement occurs within 72 hours. However, on an (inter)national level there is no consensus on the role of dexamethasone in the management of CSDH. Ideally, treatment decisions are based on the expected treatment response in individual patients.

We aimed to quantify the need for additional surgery in patients with CSDH treated with dexamethasone as a standalone therapy and to identify patient characteristics associated with additional surgery.

METHODS

Study Design

This retrospective study was conducted at the neurology departments of 3 regional hospitals in The Netherlands: Maasstad Hospital in Rotterdam, Admiraal de Ruyter Hospital in Goes, and Van Weel Bethesda Hospital in Dirksland.

Patient Population

Patients were eligible for the study if they were diagnosed with CSDH between January 1, 2008, and December 31, 2018. Patients were excluded when subdural hyperdense components were seen on the baseline computed tomography (CT) comprising more than one-third of the hematoma. For this specific analysis, we included patients receiving dexamethasone as a standalone therapy.

Treatment

From 2011 on, the use of dexamethasone as a primary treatment was incorporated in the regional CSDH guideline. This guideline advises a dexamethasone tapering course in patients with a symptomatic CSDH, defined as Markwalder Grading Scale (MGS) score 1 (minor symptoms) to 3 (severe focal signs; stuporous but responding to noxious stimuli).[27] This tapering course starts at a daily dosage of 8 mg BD (16 mg daily) on days 1–7 and thereafter tapered by half every 3 days until a dosage of 0.5 mg once daily on days 20 to 22 and ended on day 23. In the same guideline, it is advised to administer ranitidine (150 mg BD) or esomeprazole (40 mg/d) during this dexamethasone tapering course. The guideline also states that the treating physician should monitor the possible complications related to dexamethasone use, such as hyperglycemia, neuropsychiatric disorders, and infections.

Outcomes

The primary outcome of this study was surgery within 3 months. According to the guideline, surgery is indicated if clinical deterioration takes place or when no improvement occurs in the clinical condition within 72 hours after initiation of dexamethasone therapy. The indication for surgery is in practice determined after consultation between the treating neurologist and neurosurgeon.

Data Collection

Data were retrospectively collected from electronic medical records, registered on paper Clinical Registration Forms, and afterward processed in SPSS 25.0 (IBM Corp., Armonk, New York, USA). First, the diagnosis of CSDH was confirmed by a single investigator (D.C.H.) and, when in doubt, discussed with a neurosurgeon (R.D.). Baseline patient characteristics were collected and included age, sex, symptoms at diagnosis, MGS,[27] history and time point of trauma, medical history, use of medication, and CT parameters such as midline shift, hematoma thickness, side, and hematoma type (homogeneous, laminar, separated, trabecular or a combination of hematoma types) on admission CT. CT data were radiologically measured by a single investigator (D.C.H.). We further collected details on dexamethasone treatment and outcome including side effects, complications, mortality, and functional status (at 2–10 weeks and after 10 weeks). However, functional outcome was often difficult to verify since the follow-up data, as found in the electronic patient files, were often incomplete. Therefore, we could not use a validated scoring system and used the following pragmatic scale: if a patient recovered well, or had only minimal residual symptoms, we registered an overall functional status as "good." If there were still symptoms present but no additional treatment was necessary, an overall functional status of "moderate" was entered. "Poor outcome" was listed when a patient needed additional treatment. This outcome was scored up to 6 months after diagnosis. The exact dexamethasone dose was not always clear because of incomplete retrospective data. If a few days of the tapering course were missing, the dosages of these days were estimated based on the standard tapering course. Three-month mortality was scored "unknown" if no patient data were available at 3 months. The study protocol was approved by the Medical Review Ethics Committee (Rotterdam, registration number MEC-2019-0710).

Statistical Analyses

Baseline and demographic characteristics were summarized by means and standard deviations (SD) for continuous variables and numbers and percentages for categorical variables and were compared between 3 groups: patients receiving 1 dexamethasone tapering course, receiving more dexamethasone tapering courses (respectively, group DXM and group DXM-DXM), and patients who received 1 or more dexamethasone courses in combination with additional surgery (DXM-SURG). We assessed the association of the following potential predictors with additional surgery (compared with 1 or more dexamethasone courses); age, the Charlson Comorbidity Index, the MGS, the use of antithrombotic drugs (anticoagulants and antiplatelet drugs) or statins, and the baseline radiologic parameters: midline shift, hematoma thickness, side of the hematoma and hematoma type with univariable and multivariable logistic regression analysis. We presented the associations as (adjusted) odds ratios (aORs). SPSS 25.0 was used for statistical analysis.

RESULTS

Between January 1, 2008, and December 31, 2018, 484 patients were diagnosed with a CSDH, of whom 283 patients (58%) received dexamethasone as a stand-alone therapy and were included in this study (Figure 1). Of these, 146 patients (52%) received 1 dexamethasone course (DXM group), 30 patients (10%) received more dexamethasone courses (DXM-DXM group), and 107 patients (38%) received 1 or more dexamethasone courses followed by surgery (DXM-SURG group).

The mean (SD) age at diagnosis was 75 (10) years and the large majority was male ($n = 199$, 70%) (Table 1). Symptoms observed most often at diagnosis were gait disturbance ($n = 184$, 65%) and headache ($n = 148$, 52%). Most patients had an MGS of 2 ($n = 210$, 74%). A history of (minor) head trauma was present in 187 patients ($n = 66$%) with mean days (SD) between trauma and diagnosis of 50 (32). Main coexisting medical conditions were hypertension ($n = 118$, 42%), atrial fibrillation ($n = 76$, 27%), and diabetes ($n = 67$, 24%). Antithrombotics were used by 160 patients (57%). Baseline CT showed a bilateral CSDH in 92 patients (33%), a hematoma thickness of 10–20 mm in 143 patients (51%), and a homogeneous hematoma in 116 patients (41%) (Table 1).

The median (min–max) starting dose of dexamethasone was 8 (2–16) mg per day (Table 2). Mean total days (SD) and dose (SD) of dexamethasone treatment was 40 (34) days with a total of 193 (114) mg. In the DXM-SURG group, 67 patients (63%) received 1 dexamethasone tapering course, 36 patients (34%) received 2 courses, and 4 patients (4%) 3 courses of dexamethasone. Most overall common reported complications were infection ($n = 69$, 24%) and hyperglycemia ($n = 55$, 19%). The median (min–max) time to last known overall functional status was 74 (3–180) days. "Good" functional outcome within 6 months was seen in 164 patients (58%) and death within 3 months occurred in 34 patients (12%) (Table 2, causes of death in Supplementary Table 1).

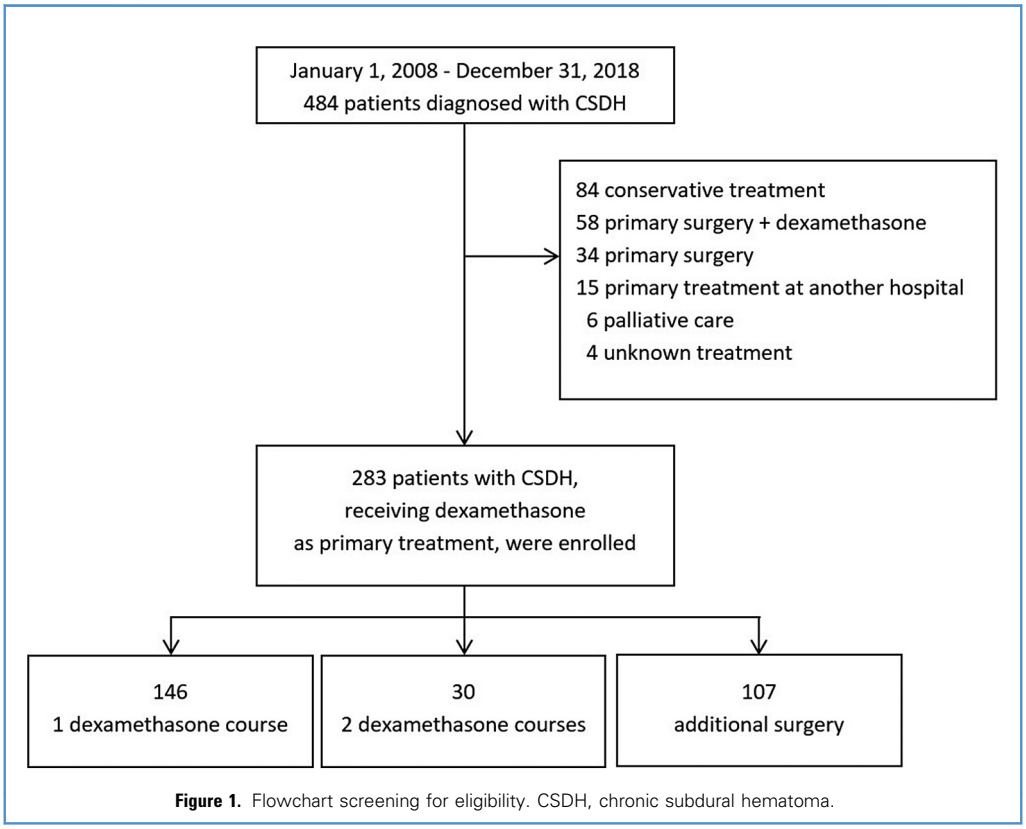

Figure 1. Flowchart screening for eligibility. CSDH, chronic subdural hematoma.

Table 1. Baseline Characteristics of Included Patients with CSDH

Characteristic	Total (N = 283)	One Dexamethasone Tapering Course (n = 146)	Dexamethasone and Additional Dexamethasone Tapering Course (n = 30)	Dexamethasone and Additional Surgery (n = 107)
Age, years	75.0 ± 10.4	74.3 ± 11.1	74.0 ± 11.6	76.1 ± 9.1
Male sex, no./total no. (%)	199/283 (70.3)	93/146 (63.7)	23/30 (76.7)	83/107 (77.6)
Charlson Comorbidity Index	4.3 ± 1.9	4.3 ± 2.1	3.9 ± 1.9	4.5 ± 1.8
Symptoms, no./total no. (%)				
Headache	148/283 (52.3)	77/146 (52.7)	20/30 (66.7)	51/107 (47.7)
Gait disturbance	184/283 (65.0)	89/146 (61.0)	14/30 (46.7)	81/107 (75.7)
Altered mental status	107/283 (37.8)	54/146 (37.0)	6/30 (20.0)	47/107 (43.9)
Hemiparesis	107/283 (37.8)	50/146 (34.2)	10/30 (33.3)	47/107 (43.9)
Speech disorder	92/283 (32.5)	49/146 (33.6)	6/30 (20.0)	37/107 (34.6)
Seizure(s)	8/283 (2.8)	8/146 (5.5)	0/30 (0)	0/107 (0)
Nausea and vomiting	55/283 (19.4)	31/146 (21.2)	9/30 (30.0)	15/107 (14.0)
Markwalder Grading Scale score, no./total no. (%)				
0: No neurologic symptoms	1/283 (0.4)	1/146 (0.7)	0/30 (0)	0/107 (0)
1: Alert, oriented. Mild symptoms such as headache	62/283 (21.9)	42/146 (28.8)	8/30 (26.7)	12/107 (11.2)
2: Drowsy or disoriented with variable deficits	210/283 (74.2)	98/146 (67.1)	20/30 (66.7)	92/107 (86.0)
3: Stuporous; responding to stimuli, severe focal signs	10/283 (3.5)	5/146 (3.4)	2/30 (6.7)	3/107 (2.8)
Known head trauma, no./total no. (%)	187/283 (66.1)	97/146 (66.4)	13/30 (43.3)	77/107 (72.0)
Days from trauma to diagnosis	50.0 ± 32.1	51.1 ± 36.6	48.9 ± 22.7	48.8 ± 27.4
Main coexisting medical conditions, no./total no. (%)				
None	20/283 (7.1)	10/146 (6.8)	3/30 (10.0)	7/107 (6.5)
Ischemic heart disease	39/283 (13.8)	17/146 (11.6)	2/30 (6.7)	20/107 (18.7)
Atrial fibrillation	76/283 (26.9)	44/146 (30.1)	8/30 (26.7)	24/107 (22.4)
Hypertension	118/283 (41.7)	58/146 (39.7)	13/30 (43.3)	47/107 (43.9)
Previous stroke	29/283 (10.2)	13/146 (8.9)	4/30 (13.3)	12/107 (11.2)
Diabetes	67/283 (23.7)	34/146 (23.3)	8/30 (26.7)	25/107 (23.4)
Hypercholesterolemia	48/283 (17.0)	20/146 (13.7)	1/30 (3.3)	27/107 (25.2)
Statin use	116/283 (41.0)	60/146 (41.1)	8/30 (26.7)	48/107 (44.9)
Antithrombotics, no./total no. (%)	160/283 (56.5)	83/146 (56.8)	17/30 (56.7)	60/107 (56.1)
Bilateral CSDH on CT scan, no./total no. (%)	92/283 (32.5)	47/146 (32.2)	10/30 (33.3)	35/107 (32.7)
Midline shift in unilateral CSDH on CT scan, mm, no./total no. (%)	8.1 ± 4.2	6.8 ± 4.2	6.6 ± 4.0	10.1 ± 3.4
<5 mm	45/191 (23.6)	35/99 (35.4)	6/20 (30.0)	4/72 (5.6)
5–10 mm	73/191 (38.2)	33/99 (33.3)	11/20 (55.0)	29/72 (40.3)
≥10 mm	71/191 (37.2)	29/99 (29.3)	3/20 (15.0)	39/72 (54.2)

CSDH, chronic subdural hematoma; CT, computed tomography.
*Hematoma thickness in bilateral CSDH: largest hematoma was included.
†Combined CSDH: combination of different CSDH types; most often seen in bilateral CSDH.

Continues

Table 1. Continued

Characteristic	Total ($N = 283$)	One Dexamethasone Tapering Course ($n = 146$)	Dexamethasone and Additional Dexamethasone Tapering Course ($n = 30$)	Dexamethasone and Additional Surgery ($n = 107$)
Missing	2/191 (1.0)	2/99 (2.0)	0/20 (0)	0/72 (0)
Hematoma thickness* on CT scan, mm, no./total no. (%)	16.5 ± 6.3	14.4 ± 6.0	14.0 ± 4.6	20.1 ± 5.6
<10 mm	39/283 (13.8)	29/146 (19.9)	5/30 (16.7)	5/107 (4.7)
10–20 mm	143/283 (50.5)	85/146 (58.2)	20/30 (66.7)	38/107 (35.5)
≥20 mm	97/283 (34.3)	30/146 (20.5)	5/30 (16.7)	62/107 (57.9)
Missing	4/283 (1.4)	2/146 (1.4)	0/30 (0)	2/107 (1.9)
Hematoma type on CT scan, no./total no. (%)				
Homogeneous	116/283 (41.0)	61/146 (41.8)	11/30 (36.7)	44/107 (41.1)
Laminar	26/283 (9.2)	11/146 (7.5)	4/30 (13.3)	11/107 (10.3)
Separated	38/283 (13.4)	10/146 (6.8)	4/30 (13.3)	24/107 (22.4)
Trabecular	42/283 (14.8)	26/146 (17.8)	4/30 (13.3)	12/107 (11.2)
Combined†	39/283 (13.8)	22/146 (15.1)	4/30 (13.3)	13/107 (12.1)
Missing	22/283 (7.8)	16/146 (11.0)	3/30 (10.0)	3/107 (2.8)

CSDH, chronic subdural hematoma; CT, computed tomography.
*Hematoma thickness in bilateral CSDH: largest hematoma was included.
†Combined CSDH: combination of different CSDH types; most often seen in bilateral CSDH.

Additional surgery occurred more often in patients with an MGS of 2 (compared with MGS 1, aOR 2.05; 95% CI 0.90–4.65), in patients using statins (aOR 2.09; 95% CI 1.01–4.33), in patients with a larger midline shift (aOR 1.10 per mm; 95% CI 1.01–1.21) and with larger hematoma thickness (aOR 1.16 per mm; 95% CI 1.09–1.23), in patients with bilateral hematoma (aOR 1.85; 95% CI 0.90–3.79), and in patients with a separated hematoma (compared with homogeneous, aOR 1.77; 95% CI 0.72–4.38) (**Table 3** and **Figure 2**).

Additional surgery was seen less frequently in patients using antithrombotics (aOR 0.45; 95% CI 0.21–0.95) and in patients with a trabecular hematoma (compared with homogeneous, aOR 0.31; 95% CI 0.12–0.77).

DISCUSSION

In this retrospective study, we analyzed 283 patients with CSDH from 3 regional hospitals receiving dexamethasone as a stand-alone therapy as primary treatment. Additional surgery was performed in a little more than one-third of all patients. The probability of additional surgery was greater in patients who were more severely affected neurologically, in bilateral hematoma, and in patients with a larger hematoma thickness and more midline shift.

Another retrospective study from the Netherlands in which primary dexamethasone was given for a median period of 12 days showed that additional surgery was performed in 50 of 60 patients (83%) with a median time between diagnosis and surgery of 6 days.[28] In our study, patients were treated with dexamethasone for a much longer period (12 vs. 30 days), fewer patients ($n = 107$, 38%) received additional surgery, and the time between diagnosis and surgery was longer in our study (6 vs. 12 days). Baseline characteristics were comparable between the studies, except for midline shift (median of 8–9 mm vs. 7mm in our study) and hematoma thickness (median of 24–25 mm vs. 16 mm in our study). In our study, 22% of patients had an MGS 1 at baseline compared with 28% in this previous study. These differences in baseline characteristics might contribute to the greater percentage of patients receiving additional surgery. However, it is also likely that part of the differences is explained by the decision of the treating physician and by differences in opinion on how long surgery can be awaited. Also, a difference in dosage and length of the dexamethasone tapering courses can influence the risk of additional surgery.

Of all patients with CSDH primarily treated with a dexamethasone tapering course, one-half did not require additional treatment (no additional dexamethasone nor additional surgery). In this group, more than one-half had a "good" outcome within 6 months. Patients with 1 dexamethasone course were admitted to the hospital for a mean of 10 days, and fewer complications occurred in this group of patients compared with those requiring additional treatment with either dexamethasone or surgery.

We did identify subgroups of patients in whom dexamethasone as standalone therapy might not be a desirable primary treatment option, such as patients with greater MGS (grade 2-3). This likely represents that more severely affected patients require different

Table 2. Description of Treatment and Outcome

Characteristic	Total (N = 283)	One Dexamethasone Tapering Course (n = 146)	Dexamethasone and Additional Dexamethasone Tapering Course (n = 30)	Dexamethasone and Additional Surgery (n = 107)
Dexamethasone starting dose, mg/daily, median (min-max)	8 (2—16)	8 (2—16)	8 (2—16)	12 (4—16)
Dexamethasone bolus				
Mg, mean ± SD	10.4 ± 2.0	10.7 ± 2.4	9.6 ± 0.8	10.4 ± 2.0
no./total no. (%)	68/283 (24.0)	23/146 (15.8)	10/30 (33.3)	35/107 (32.7)
Amount of dexamethasone treatments within 3 months, no./total no. (%)				
1	213/283 (75.3)	146/146 (100.0)	n/a	67/107 (62.6)
2	66 (23.3)	n/a	30/30 (100.0)	36/107 (33.6)
3	4 (1.4)	n/a	0/30 (0)	4/107 (3.7)
Dexamethasone, total days, mean ± SD	40.4 ± 34.1	41.3 ± 37.6	73.7 ± 33.9	29.9 ± 20.7
Dexamethasone, total dose, mg, mean ± SD	192.5 ± 114.3	170.4 ± 113.9	295.1 ± 120.1	192.9 ± 97.0
Admission, total days, mean ± SD	14.5 ± 12.5	9.8 ± 8.9	14.3 ± 13.5	20.9 ± 13.7
Diagnosis to surgery, days, mean (SD) / median (min—max)	n/a	n/a	n/a	23.0 ± 26.5 / 12
Cessation of anticoagulants/antithrombotics, total days mean ± SD	74.7 ± 140.9	83.8 ± 160.5	91.9 ± 76.4	62.5 ± 129.8
Complications within 3 months, no./total no. (%)				
Infection	69/283 (24.4)	23/146 (15.8)	12/30 (40.0)	34/107 (31.8)
Hyperglycemia	55/283 (19.4)	25/146 (17.1)	7/30 (23.3)	23/107 (21.5)
Pulmonary embolism	5/283 (1.8)	3/146 (2.1)	2/30 (6.7)	0/107 (0)
Thrombotic events (other than lung)	18/283 (6.4)	7/146 (4.8)	5/30 (16.7)	6/107 (5.6)
Seizure	12/283 (4.2)	4/146 (2.7)	0/30 (0)	8/107 (7.5)
Dexamethasone side effects within 3 months, no./total no. (%)				
Mood disorder	18/283 (6.4)	11/146 (7.5)	2/30 (6.7)	5/107 (4.7)
Sleeping disorder	6/283 (2.1)	4/146 (2.7)	1/30 (3.3)	1/107 (0.9)
Eating disorder	9/283 (3.2)	7/146 (4.8)	1/30 (3.3)	1/107 (0.9)
Last known overall functional status within 6 months, no./total no. (%)				
Good	164/283 (58.0)	90/146 (61.1)	14/30 (46.7)	60/107 (56.1)
Moderate	41/283 (14.5)	17/146 (11.6)	6/30 (20.0)	18/107 (16.8)
Poor	23/283 (8.1)	6/146 (4.1)	4/30 (13.3)	13/107 (12.1)
Death	34/283 (12.0)	17/146 (11.6)	5/30 (16.7)	12/107 (11.2)
Unknown	21/283 (7.4)	16/146 (11.0)	1/30 (3.3)	4/107 (3.7)

SD, standard deviation.

treatment. The use of statins also was related to a greater risk of additional surgery. This is in contrast to previous studies that suggest that atorvastatin accelerated the absorption of CSDH and decreased the risk of recurrence and the risk of surgery.[29-32] Also, in mice models, atorvastatin was found to have anti-inflammatory and antiangiogenic effects.[14,33] However, a proangiogenic effect of atorvastatin also has been described.[14,34,35] Recently, atorvastatin has been suggested as a safe and efficacious nonsurgical alternative in the treatment of chronic subdural hematoma.[36] Also, a combined treatment of atorvastatin and low-dose dexamethasone is being investigated and results are awaited.[37] Our sample, however, did not allow analysis of this group, because only 25 of 283 patients (8.8%) used atorvastatin at diagnosis. Further research on this potential predictor is necessary.

Table 3. Factors Associated with Surgery

	Univariable		Multivariable	
	OR (95% CI)	*P* Value	aOR (95% CI)	*P* Value
Age, years	1.02 (0.99–1.04)	0.145	1.01 (0.97–1.05)	0.546
Charlson Comorbidity Index at admission	1.06 (0.94–1.20)	0.334	1.07 (0.86–1.35)	0.536
Markwalder Grading Scale at admission				
Grade 1*	ref	0.002	ref	0.171
Grade 2	3.31 (1.67–6.58)		2.05 (0.90–4.65)	
Grade 3	1.82 (0.41–8.09)		1.03 (0.19–5.70)	
Use of antithrombotics at admission	0.97 (0.60–1.58)	0.903	0.45 (0.21–0.95)	0.036
Use of statins at admission	1.29 (0.79–2.10)	0.302	2.09 (1.01–4.33)	0.047
CT at admission				
Midline shift, mm	1.18 (1.11–1.26)	<0.0001	1.10 (1.01–1.21)	0.037
Hematoma thickness, mm†	1.18 (1.13–1.24)	<0.0001	1.16 (1.09–1.23)	<0.0001
Uni/bilateral				
Unilateral	ref	0.955	ref	0.094
Bilateral	1.02 (0.61–1.69)		1.85 (0.90–3.79)	
Hematoma type				
Homogeneous	ref	0.006	ref	0.013
Laminar	1.20 (0.51–2.85)		0.60 (0.22–1.66)	
Separated	2.81 (1.31–5.99)		1.77 (0.72–4.38)	
Trabecular	0.66 (0.30–1.41)		0.31 (0.12–0.77)	
Combined	0.82 (0.38–1.76)		0.62 (0.24–1.61)	
Unknown	0.26 (0.07–0.92)		0.15 (0.03–0.85)	

OR, odds ratio; CI, confidence interval; aOR, adjusted odds ratio; CT, computed tomography; MGS, Markwalder Grading Scale; CSDH, chronic subdural hematoma.
*One patient with MGS 0 was included in the MGS 1 group. Symptoms were present in this patient before visiting the Emergency Department, but not at diagnosis.
†Hematoma thickness in bilateral CSDH: largest hematoma was included. Multivariable model contains all listed factors.

The following baseline radiologic characteristics also seemed to be related to a greater risk of additional surgery: patients with a bilateral CSDH, with a larger midline shift, a larger hematoma thickness, and a separated hematoma type. The former 3 may, just as the MGS, represent "severity." Regarding the hematoma type, it is believed that CSDH develops initially as a homogenous fluid collection, sometimes progressing to a laminar type. The mature state follows, which is characterized by the separated stage, finally resulting in the trabecular stage after which absorption follows.[38] CSDH may be self-limiting, but it is often seen that this pathophysiological process degenerates into a vicious cycle.[14] This natural development within the hematoma can be the explanation of the results in our study that separated hematomas more often need additional surgery compared to the trabecular type.

Additional surgery also was less frequent in patients using antithrombotics. It is reported that the use of antithrombotic agents increases the risk of CSDH recurrence.[39,40] Therefore, we can only speculate about the underlying cause of this finding. We would have expected that antithrombotics cause microbleeds and with that a perpetuating vicious cycle. However, temporary cessation of antithrombotic medication could be a factor in stopping this vicious cycle. We also expected that treating physicians would operate on these patients sooner because they do not want to discontinue the antithrombotics for too long.

Using baseline information to identify patients treated with dexamethasone that are associated with a low risk of additional treatment and a high likelihood of a favorable outcome might eventually inform individual treatment decisions on dexamethasone versus surgery. Since treatment decisions should not be based on single characteristics, such predictive characteristics are combined in prognostic models to predict outcomes for alternative treatment options for individual patients.[41] However, this requires high-quality (randomized) data and larger sample sizes. Our study informs on what baseline predictors to consider in future studies. It is expected that more randomized data will be published on CSDH in the coming years, which can be used for predictive modeling for more personalized treatment of patients with CSDH.[42] Also, data from CSDH studies are known to be

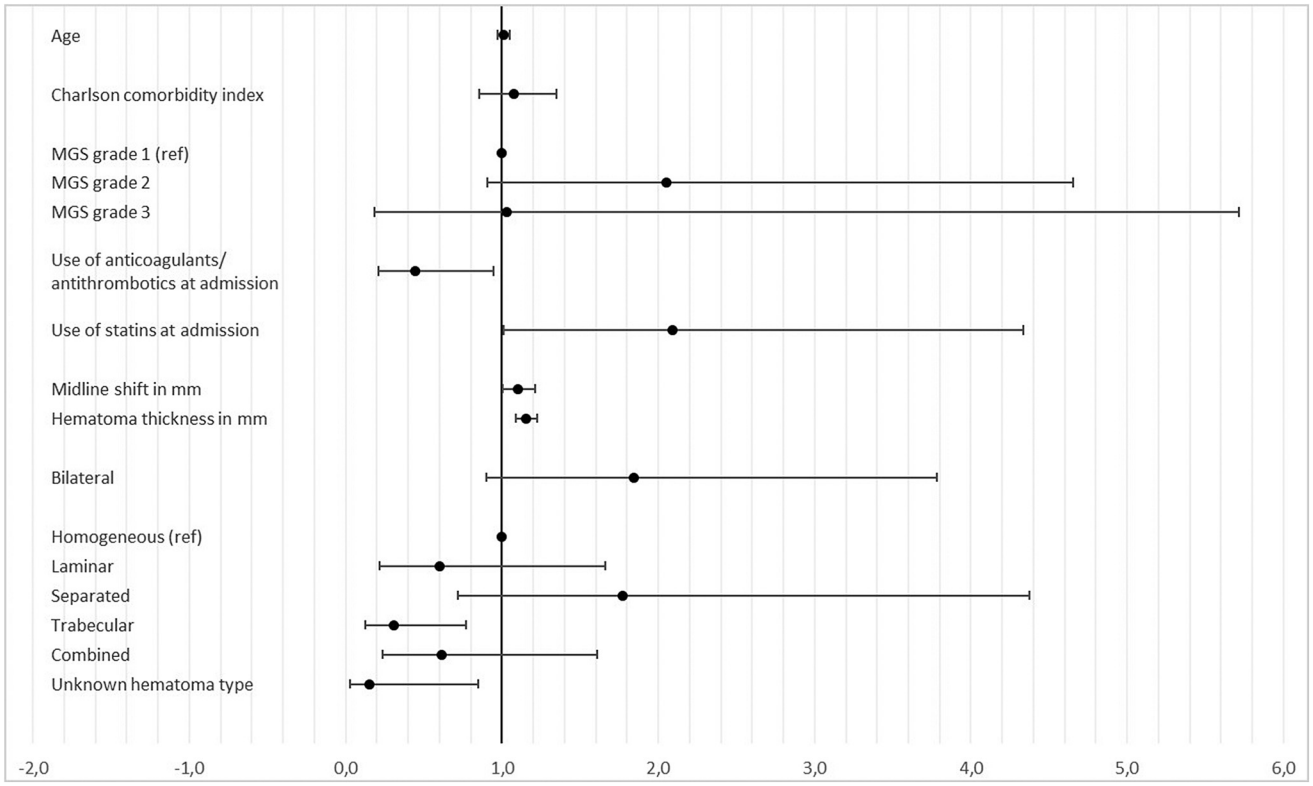

Figure 2. Multivariable odds ratios and confidence intervals for the association between baseline characteristics and surgery. MGS, Markwalder Grading Scale.

heterogeneous[43] and can therefore not easily be compared. When predictors are presented more homogeneously, they are more reliable to be used in prediction modeling. Therefore, the CODE-CSDH group is working on the development of a core outcome set and baseline data elements.[44]

Some limitations of our study should be discussed. The first limitation is the retrospective design of this study. This potentially affects patient inclusion, most likely missing patients who had a CSDH, as well as data quality. Functional outcome, for example, measured by the modified Rankin Scale, could not reliably be collected from all the patient files. Also, possibly not all complications were registered in the patient files, resulting in an underestimation of most likely the less severe complications. Infection and hyperglycemia occurred most often. Another limitation is that patients were treated according to the decision of their physician. Despite the guideline on CSDH management being available since 2011, physicians might register patients sooner for surgery when they notice a larger midline shift, larger hematoma thickness, or a bilateral hematoma on CT, even if clinical symptoms are comparable with patients suffering from smaller CSDHs. It may as well be the other way around. A patient might benefit from surgery, but the treating physician, the patients, or the next-of-kin might not concur with this option. Therefore, the indication for additional treatment is difficult to objectify in a retrospective patient population.

One of the strengths of this study is that the data were obtained from a region where treating physicians are used to prescribing dexamethasone because this has been used in daily clinical practice for over 40 years. Therefore, additional surgery was not required because of a lack of experience with the use of dexamethasone. In addition, the use of a dexamethasone tapering course in the management of CSDH is described in a regional guideline which states how long the treating physician can continue a "observe-and-wait" policy and when to consult a neurosurgeon.

CONCLUSIONS

More than one-third of patients with CSDH primarily treated with dexamethasone received additional surgery. These patients were neurologically more severely affected and had larger hematomas.

Further prospective research is needed to identify patients in whom direct surgery is indicated versus those in whom dexamethasone might be sufficient, to ideally move towards personalized treatment of CSDH.

CRediT AUTHORSHIP CONTRIBUTION STATEMENT

Dana C. Holl: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Writing — original draft, Project administration, Funding acquisition. **Rahman Fakhry:**

Investigation, Writing — original draft, Formal analysis. **Clemens M.F. Dirven:** Conceptualization, Writing — review & editing, Supervision, Funding acquisition. **Florien A.L. te Braake:** Investigation, Writing — review & editing. **Orit K. Begashaw:** Investigation, Writing — review & editing. **Walid Moudrous:** Investigation, Writing — review & editing. **S. Mirjam Droger:** Investigation, Writing — review & editing. **Nabil Asahaad:** Investigation, Writing — review & editing. **Christiaan de Brabander:** Investigation, Writing — review & editing. **Gerben J.J. Plas:** Investigation, Writing — review & editing. **Bram Jacobs:** Writing — review & editing, Supervision. **Joukje van der Naalt:** Writing — review & editing, Supervision. **Heleen M. den Hertog:** Writing — review & editing, Supervision. **Niels A. van der Gaag:** Writing — review & editing, Supervision. **Korné Jellema:** Writing — review & editing, Supervision. **Ruben Dammers:** Conceptualization, Writing — review & editing, Supervision, Funding acquisition. **Hester F. Lingsma:** Conceptualization, Methodology, Formal analysis, Writing — original draft, Supervision, Funding acquisition.

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SUPPLEMENTARY DATA

Supplementary Table 1. Causes of Death

One Dexamethasone Tapering Course ($N = 17$)	Dexamethasone and Additional Dexamethasone Tapering Course ($N = 5$)	Dexamethasone and Additional Surgery ($N = 12$)
• Status epilepticus. • Arrhythmia. • Pneumonia; surgery not possible due to overall pulmonary condition. • Died in a nursing home 1 week after cessation of dexamethasone. • Medical history of coronary artery disease and bradycardia with a "severely poor prognosis"; urinary tract infection at discharge. • Autopsy: gastric/duodenal ulcer, aspiration of blood. • Pulmonary emboli after discontinuation of anticoagulants. On the waiting list for surgery, but clinical situation declined in the meantime. • Congestive heart failure due to cardiac ischemia. • Patient was on therapeutic heparin. • COPD exacerbation. • End-stage liver failure in cryptogenic liver cirrhosis causing hepatic encephalopathy. • No recovery and additional delirium. Surgery was rejected by the next-of-kin due to comorbidity. • Congestive heart failure at admission; this increased and was the cause of death. • Cardiac asthma. • Cause unknown (4 times)	• Surgery was rejected by the next-of-kin due to comorbidity. • Cause unknown. Differential diagnosis: Urinary tract infection or increasing CSDH. • Hospital-acquired pneumonia. • Differential diagnosis: Pulmonary embolism or congestive heart failure. • Combination of multiple complications: pneumonia, sepsis and vascular problems.	• Surgery was rejected by the patient. Hyperkalemia in metabolic acidosis with a medical history of chronic renal insufficiency. • Increased CSDH, no additional treatment due to comorbidity. • Pneumonia, various antibiotics used. Patient asked for palliative care. • Operated 2 times, both complicated by a rebleed. • Cause unknown. Discharged to a nursing home while suffering from delirium. • Multiorgan failure; sepsis due to an already purulent wound at the elbow at diagnosis. • Lung carcinoma. • Refractory stage of septic shock due to empyema. Developed a complex partial status epilepticus. Treatment was discontinued. • Differential diagnosis: Pulmonary embolism. Died postoperatively on the postanesthesia care unit; 3 resuscitation attempts. • Crural arterial occlusion with compartment syndrome requiring thrombectomy and fasciotomy. Eventually palliative care. • Liver metastases from esophageal carcinoma. • Cause unknown.

COPD, chronic obstructive pulmonary disease; CSDH, chronic subdural hematoma.