Universiteit
Leiden
The Netherlands

Chronic subdural hematoma: tailoring treatment

Miah, I.P.

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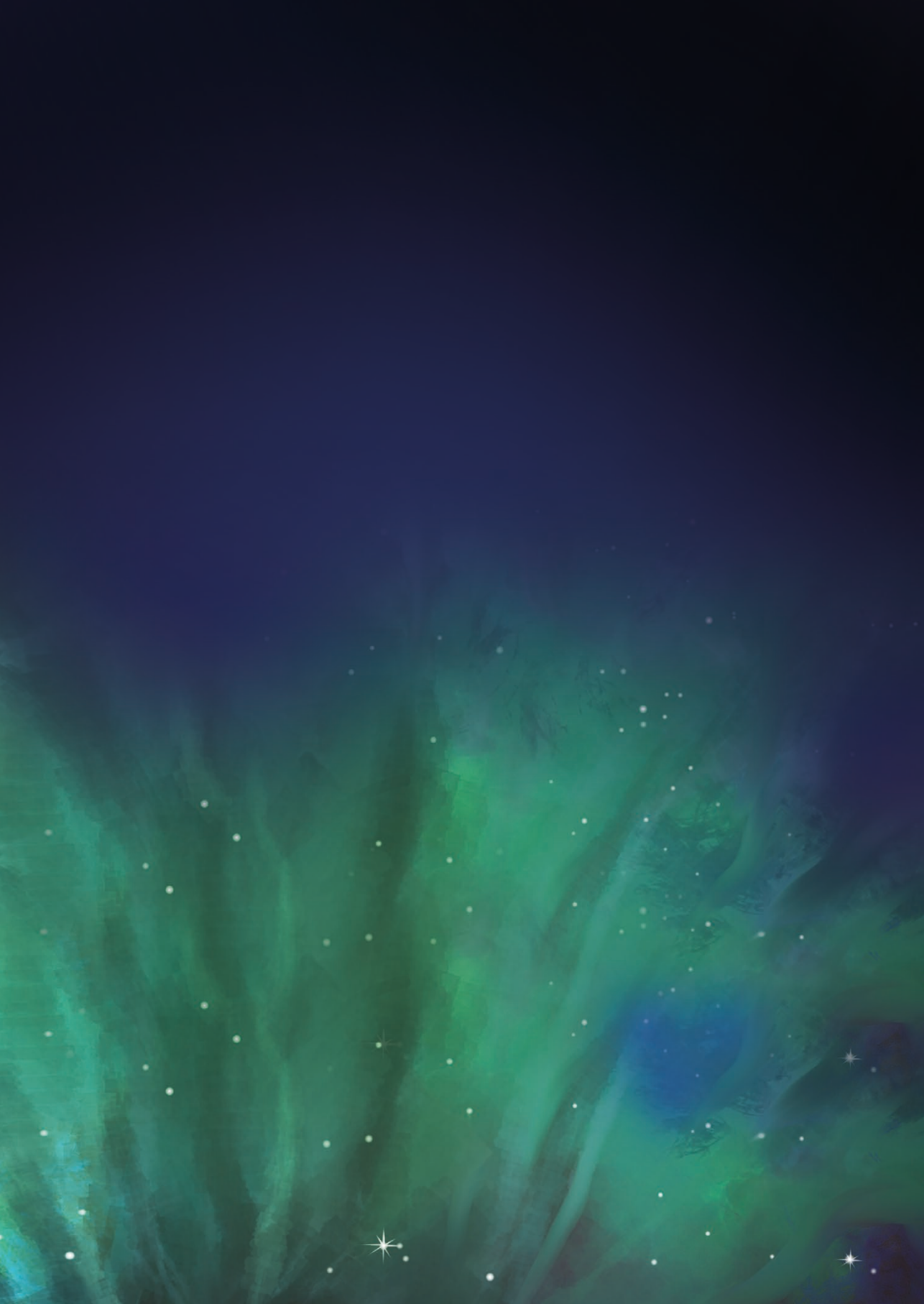

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Change in hematoma size after dexamethasone therapy in chronic subdural hematoma subtypes: A prospective study in symptomatic patients

Miah IP, Blanter A, Tank Y, van Zwet EW, Rosendaal FR, Peul WC, Dammers R, Holl DC, Lingsma HF, den Hertog HM, van der Naalt J, Jellema K, van der Gaag NA.

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Abstract

Background

The main treatment strategy for chronic subdural hematoma is surgical intervention or conservative approach with dexamethasone. Recent trials revealed dexamethasone therapy to be an ineffective treatment in symptomatic patients with chronic subdural hematoma. Whether the efficacy of dexamethasone therapy differs in radiological hematoma subtypes is unknown. The aim of this substudy was to identify which hematoma subtype might be favorable for dexamethasone therapy.

Methods

As part of a randomized controlled trial (RCT) symptomatic chronic subdural hematoma patients received 19-days dexamethasone therapy. The primary outcome measure was the change in hematoma size as measured on follow-up computed tomography (CT) after two weeks of dexamethasone in eight hematoma (architectural and density) subtypes: homogeneous total, laminar, separated and trabecular architecture types, and homogeneous hypodense, -isodense, -hyperdense and mixed density types. We analyzed hematoma thickness, midline shift and volume using multi-variable linear regression adjusting for age, sex and baseline value of the specific radiological parameter.

Results

From September 2016 until February 2021, 85 patients were included with a total of 114 chronic subdural hematoma. The mean age was 76 years and 25% were women. Larger decrease in hematoma thickness and midline shift was revealed in hematoma without hyperdense components compared to hematoma with hyperdense components (adj. b -2.2 mm, 95% CI -4.1 to -0.3 and adj. b -1.3 mm, 95% CI -2.7 to 0.0 respectively). Homogeneous hyperdense hematoma was a prognostic factor of no neurological improvement (odds ratio [OR] 0.08, 95% CI 0.0 to 0.8) compared to homogeneous hypodense hematoma. Additional surgery was performed in 57% of patients with the highest observed rate (80%) in separated hematoma.

Conclusion

Largest hematoma reduction was observed in chronic subdural hematoma without hyperdense components after dexamethasone therapy. Secondary surgery was highest in separated hematoma. Evaluation of these parameters can be part of an individualized treatment strategy.

Introduction

Chronic subdural hematoma is a frequently encountered neurological and neurosurgical disease with an increasing prevalence in the elderly [1-3]. The preceding event is generally a head trauma with a higher risk of chronic subdural hematoma development in patients using antithrombotic therapy compared to patients without therapy [4-5]. The diagnosis is established with computed tomography (CT) which reveals a crescent shaped fluid collection in the subdural space with a hematoma density that varies from hypo- to slightly hyperdense relative to adjacent brain parenchyma [6]. Hematoma density appearance on CT reflects the chronicity of the hemorrhagic degradation products; with hypodense areas representing hematoma of older age and hyperdense components more recent or active bleeding [7-9]. In addition, CT architecture types have been proposed to describe the natural development of chronic subdural hematoma from a homogeneous type, into a laminar, then separated type and finally absorbed as a trabecular hematoma [10].

The main treatment strategy of chronic subdural hematoma consists of surgical evacuation through burr-hole craniostomy which provides an immediate relief of pressure on the ipsilateral hemisphere, resulting in a fast neurological improvement [11]. However, conservative strategies are proposed as monotherapy in an attempt to avoid surgery and as adjunctive therapy to surgery to lower the post-operative recurrence risk of 2-33% [12-24]. The main target of these non-surgical strategies is the postulated inflammatory response in the subdural space, which could be responsible for hematoma persistence and enlargement [25-28]. The corticosteroid dexamethasone is mostly applied in current clinical practice. Depending on the extent of clinical and radiological improvement during the first days to weeks, the treating physician decides whether the dexamethasone (tapering) scheme can be safely completed or additional surgery is required to achieve good recovery. Recent randomized controlled trials (RCT) however revealed poorer effect of dexamethasone therapy on functional outcome compared to surgery in symptomatic patients (IP Miah, Dexamethasone versus surgery for chronic subdural hematoma, DECSA-trial: a randomized controlled trial, 2022, in submission) [29-30]. A proportion of patients in the DECSA trial (39%) did achieve a favorable functional outcome on dexamethasone monotherapy. In surgical studies, higher recurrence rates and poorer functional outcome in chronic subdural hematoma with hyperdense components or a separated or laminar architecture type have been identified [31]. The response of specific chronic subdural

hematoma subtypes to dexamethasone monotherapy has not been investigated. Theoretically, the response to dexamethasone therapy could be different in light of the inflammatory pathogenesis hypothesis with radiological subtypes reflecting a different hematoma age and stage of inflammation. Little is known about the radiological and associated clinical short-term effects of initial dexamethasone therapy. This information however, is essential in defining subsequent treatment. The aim of this study is to identify which radiological chronic subdural hematoma subtype is most responsive to dexamethasone therapy as evaluated on CT and whether this subsequently contributes to clinical improvement.

Materials and methods

Study design and population

This study is part of a recently completed multicenter RCT: Dexamethasone therapy versus surgery for chronic subdural hematoma (DECSA trial) [32]. Participating centers in this substudy were three Dutch neurotrauma centers: Haaglanden Medical Center The Hague, Haga Teaching Hospital The Hague, and Leiden University Medical Center. Symptomatic chronic subdural hematoma patients with a symptom severity score of 1 (headache only), 2 (focal neurological deficits) or 3 (severe focal deficit with impaired consciousness) on the Markwalder Grading Scale, were eligible for inclusion [33]. Patients with a Markwalder Grading Scale score 0 (asymptomatic) and 4 (comatose) were excluded. In addition to the in- and exclusion criteria of the DECSA-trial, patients were eligible if a baseline CT was present and patients received dexamethasone treatment after randomization [32].

Study treatment

Dexamethasone therapy, combined with a proton-pump inhibitor (pantoprazole 40 mg daily), was administered twice daily in a daily dosage of 16 mg on days 1 to 4, 8 mg on days 5-7, 4 mg on days 8-10, 2 mg on days 11-13, 1 mg on days 14-16, and 0.5 mg on days 17-19 and stopped at day 20, resulting in a total amount of 110.5 mg dexamethasone. Dexamethasone therapy was discontinued for the following reasons: (1) insufficient improvement of neurological condition two weeks after initiation of dexamethasone therapy with unchanged or increased hematoma on follow-up cranial CT, (2) clinical deterioration observed by neurological examination at any time, (3) the occurrence of severe dexamethasone-related side effects or complications and (4) pre-term

discontinuation of dexamethasone treatment left to the discretion of the treating physician when severe clinical condition with relevant comorbidities interfered with recovery. In the latter group, additional surgery was then deemed to be beneficial and the safest option for patient recovery. At the primary follow-up at two weeks, a follow-up CT and neurological examination was performed to evaluate the radiological and clinical change in order to decide whether additional surgery by burr hole craniostomy was deemed necessary.

Study procedures and data collection

For this substudy, patients were evaluated at presentation, during admission, discharge and at two weeks (or last day of dexamethasone monotherapy, whichever came first) from randomization combined with follow-up CT at two weeks. If dexamethasone therapy was prematurely terminated, the last day of dexamethasone treatment with corresponding follow-up CT was maintained as primary follow-up evaluation. The following radiological parameters at diagnosis and follow–up were assessed: hematoma laterality, hematoma architecture and density type, hematoma size by measurement of hematoma thickness, midline shift and volume. Hematoma volume was measured using the ABC/2 – formula [34]. Hematoma architecture subtypes were reported using the architectural classification as described by Nakaguchi: (A) homogeneous total, (B) laminar, (C) separated and (D) trabecular (table 1, figure 1) [10]. Hematoma density subtypes were categorized as hematoma without hyperdense components including (E) homogeneous hypodense and (F) -isodense hematoma and hematoma with hyperdense components consisting of homogeneous hyperdense (G), and (H) mixed density hematoma (figure 1). Radiological parameters were assessed by one vascular neurologist (IPM) and

Table 1. Hematoma classification by Nakaguchi (architecture subtypes)

Architecture types	Description
Homogeneous - total	Hematoma with complete homogeneous density, including homogeneous hypo-, iso- and hyperdense hematoma
Laminar	Hematoma with thin high-density layer along the inner membrane (against the surface of the cortex)
Separated	Hematoma with two components of different densities with a clear boundary between them, resulting in a lower density component above a higher density component. If this boundary is mingled at the border, this is called a gradation type
Trabecular	Hematoma with inhomogeneous components and a high-density septum running between the inner and outer hematoma membrane

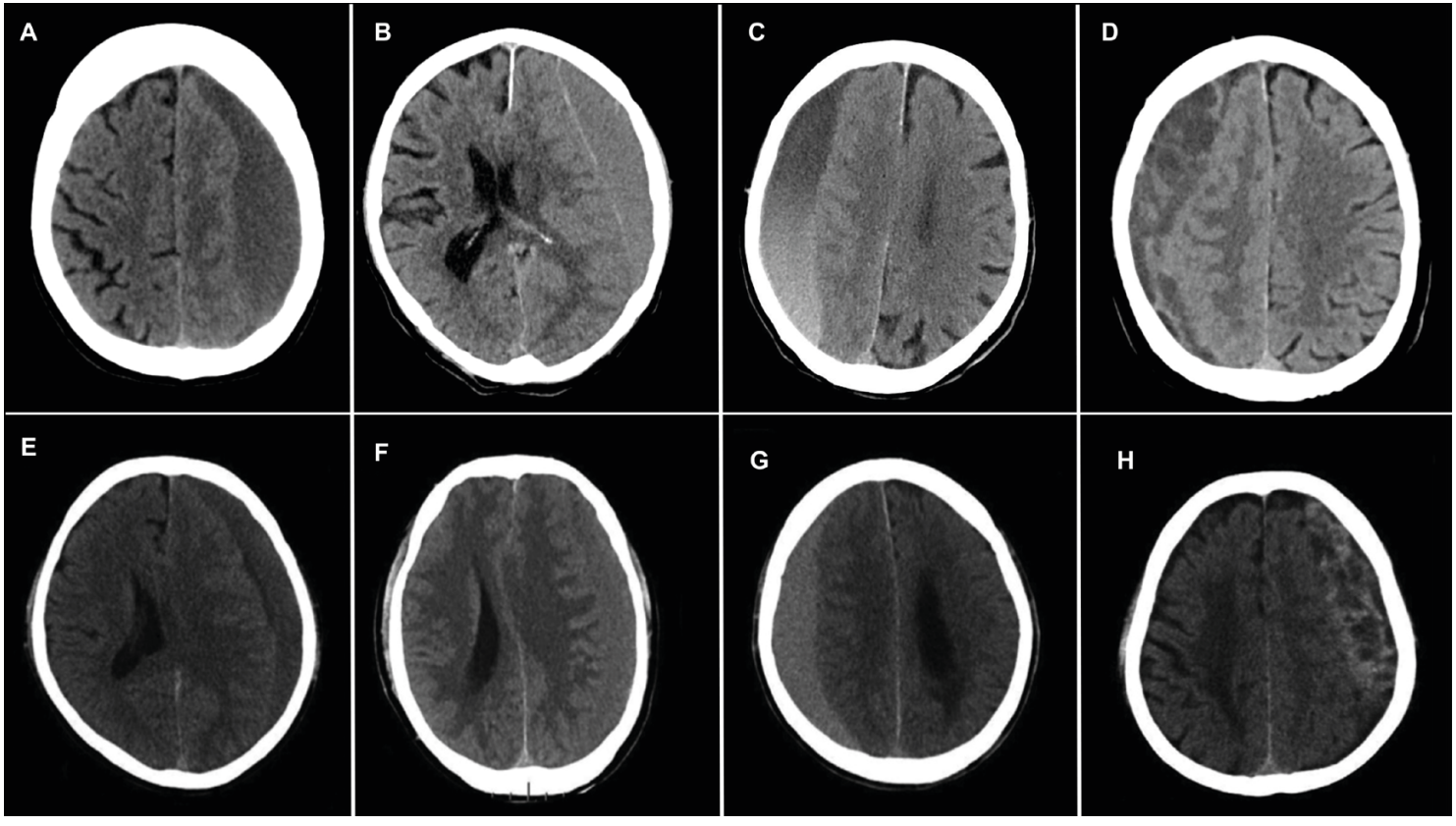

Figure 1. Radiological hematoma subtypes by architecture and density. A: homogeneous architecture (hypodense case); B: laminar architecture; C: separated architecture; D: trabecular architecture; E: homogeneous hypodense density; F: homogeneous isodense density; G: homogeneous hyperdense density; H: mixed density.

emergency radiologist (YT) independently. In case of disagreements, consensus was reached. Neurological outcome at primary follow-up evaluation was assessed by neurological examination combined with the Markwalder Grading Scale score and subsequently scored into three categories, after comparison to neurological function at presentation: i. no change, ii. improvement, iii. deterioration. Based on the extent of clinical and radiological improvement, the need for additional surgery was determined by the treating physician. Additionally, functional outcome expressed by the modified Rankin Scale score was assessed at primary follow-up. The study protocol was approved prior to data collection by the local Medical Ethics Committee (METC Zuid West Holland, No. 16-024). Ethics review criteria conformed to the Helsinki declaration. All patients gave written informed consent. Study data were processed in a clinical trial management system (Castor EDC, Amsterdam, The Netherlands).

Study outcomes

Primary outcome was to identify which chronic subdural hematoma subtype was the most responsive to dexamethasone therapy at the primary evaluation moment of dexamethasone therapy at two weeks, by examining the change in the following radiological parameters: hematoma thickness (mm), midline shift (mm) and hematoma volume (mL).

Secondary outcome measures were change in neurological function, symptom severity (Markwalder Grading Scale score) and functional outcome (modified Rankin Scale score) at the primary follow-up evaluation at two weeks, clinical onset of improvement on dexamethasone (days) and number of patients requiring additional surgery (dexamethasone failure).

Statistical analysis

Summaries using appropriate descriptive statistics were provided for all clinical and radiological variables, including demographic and baseline characteristics. In addition to the summary data in tables, graphical presentations of summary data were provided when indicated using SPSS 27.0 (IBM Corporation, New York) and GraphPad Prism 8.0 (GraphPad Software, San Diego, California USA). Multivariable linear regression analysis was performed to evaluate the change in primary radiological outcome (regression coefficient, b) in each hematoma subtype (A-H) as well as combined density subtypes indicating hematoma without (type E, F) and with (type G, H) hyperdense components. All regression analyses were conducted, adjusting for age, sex and baseline value of the specific radiological parameter assessed. Regression analysis of the primary

(radiological) outcome was performed in all chronic subdural hematoma (uni- and bilateral combined). Regression analysis regarding (the change in) secondary clinical parameters in relation to hematoma subtype and change in hematoma size (hematoma thickness, midline shift, hematoma volume), were assessed by evaluating the hematoma on the symptomatic side in bilateral chronic subdural hematoma since this side contributed to the symptoms. If the symptomatic side was unknown, the side that caused midline shift, thus contributing the most to the clinical condition, was used for analysis. A p-value of less than 0.05 was used to indicate statistical significance.

Results

Baseline

In total 180 patients were screened for this study (figure 2). Of these, 85 patients fulfilled the study criteria and could be included during the entire study period of the DECSA-trial from September 2016 until February 2021 (table 2). The mean age was 76 years (Standard Deviation [SD] +/- 11), with 21 female patients (25%). Anti-thrombotic therapy was used in 50 patients (59%) and discontinued

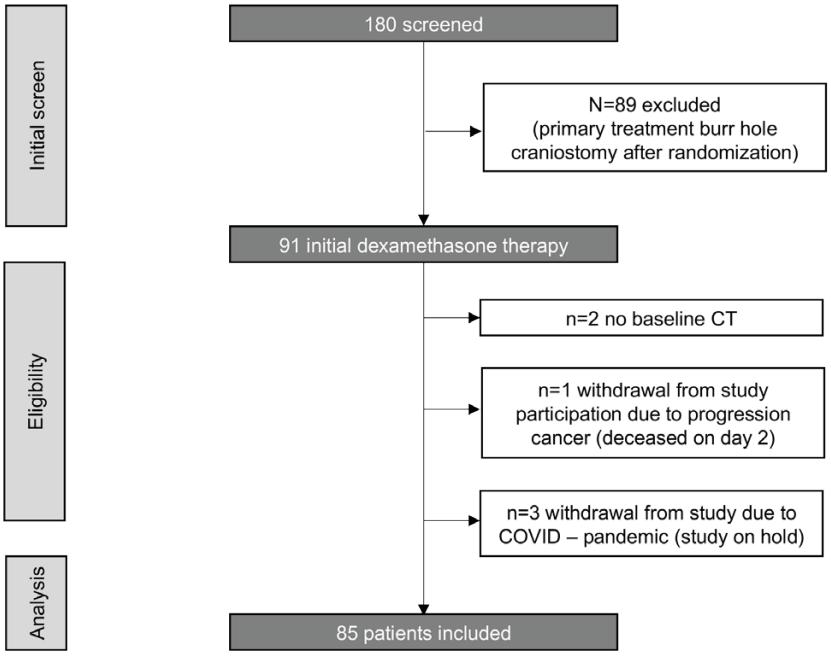

Figure 2. CONSORT flowchart of patient inclusion.

Table 2. Baseline characteristics.

Baseline characteristic	CSDH patients (n=85)
Sex, female (%)	21 (25)
Age, y, mean (SD)	76 (11)
Trauma, present (%)	69 (81)
Duration trauma – diagnosis, d, median (IQR)	42 (20-59)
Duration symptoms – diagnosis, d, median (IQR)	10 (4-23)
Anti-thrombotic therapy, total n (%)	50 (59)
PAI	24/50 (48)
OAC	26/50 (52)
Ceased at diagnosis	50/50 (100)
Comorbidities	
Cardiac history	41 (48)
Hypertension	41 (48)
Stroke	15 (18)
Venous thrombo-embolism	4 (5)
Diabetes mellitus	13 (15)
Neurodegenerative	7 (8)
Malignancies	15 (18)
Clinical condition prior to CSDH	
mRS 0 – 2, n (%)	71/85 (84)
mRS 3 – 5, n (%)	14/85 (16)
Symptom severity at admission	
MGS 1, n (%)	12/85 (14)
MGS 2, n (%)	73/85 (86)
CSDH laterality	
unilateral (%) / bilateral (%)	56 (66) / 29 (34)
Total CSDH, n	114
Hematoma size, overall	
Thickness, mm, mean (SD)	21 (7)
Midline shift, mm, mean (SD)	9 (4)
Volume, mL, mean (SD)	120 (67)
Hematoma appearance subtypes[a]	
Homogeneous, n (%)	56/114 (50)
Laminar, n (%)	8/114 (7)
Separated, n (%)	20/114 (18)
Trabecular, n (%)	30/114 (26)
Hematoma density subtypes[a]	
Homogeneous hypodense, n (%)	12/114 (11)
Homogeneous isodense, n (%)	25/114 (22)
Homogeneous hyperdense, n (%)	19/114 (17)
Mixed density, n (%)	58/114 (51)

immediately at diagnosis. Symptom severity at diagnosis was Markwalder Grading Scale score 1 in 12 (14%) and Markwalder Grading Scale score 2 in 73 (86%) patients. 114 chronic subdural hematoma were assessed of which 56

(66%) were unilateral (table 2). Of the hematoma architectural subtypes, 56 were homogeneous (A), 8 laminar (B), 20 separated (C) and 30 trabecular (D). Density type classification showed 12 homogeneous hypo- (E), 25 iso- (F) and 19 hyperdense hematoma (G), and 58 mixed density hematoma (H).

Follow-up

Median time to primary follow-up evaluation was 15 days (1-86 range, IQR 12-18; table 3). Due to clinical deterioration, earlier evaluation was performed within 7 days in 10 patients (12%). One patient with good recovery (Markwalder Grading Scale score 0) did not manage to appear at follow–up evaluation (with CT) on day 14, but on day 86. Dexamethasone treatment schedule of 19-days was completed in 60 (71%) patients, and terminated earlier in 25 (29%) patients when the clinical situation prompted for additional surgery within two weeks. Median administered dexamethasone dose was 102.5 mg (IQR 100.2 – 110.5).

Table 3. Clinical outcome at primary follow-up – two weeks

Parameter	CSDH patients (n=85)
Total amount dexamethasone (mg), median (min-max; IQR)	102.5 (16-148.5; 100.2-110.5)
Time to primary CT follow-up, d, median (min-max; IQR)	15 (1-86; IQR 12-18)
Symptom severity at two weeks[a]	
MGS 0, n (%)	12/85 (14)
MGS 1, n (%)	25/85 (29)
MGS 2, n (%)	42/85 (49)
MGS 3, n (%)	5/85 (6)
MGS 4, n (%)	1/85 (1)
Change in neurological function[a]	
Improvement, n (%)	47/85 (55)
No change, n (%)	11/85 (10)
Deterioration, n (%)	27/85 (24)
Duration until improvement, d, median (min-max; IQR)	2 (1-17; 1-4)
Need for additional surgery, n (%)	48 (57)
Duration until surgery, d, median (min-max; IQR)	16 (1-71; IQR 8-28)
Indication additional surgery[a]	
Clinical deterioration, n (%)	32/48 (67)
Unchanged clinical status, n (%)	5/48 (10)
Minimal clinical improvement, n (%)	11/48 (23)
Radiological hematoma increase, n (%)	17/48 (35)
Unchanged radiological hematoma, n (%)	21/48 (44)
Minimal radiological hematoma decrease, n (%)	10/48 (21)

IQR = interquartile range; MGS = Markwalder Grading Scale score. [a]: because of rounding percentages may not add up to 100.

Radiological hematoma evolution

At follow-up, 5 of the 114 chronic subdural hematoma showed complete hematoma resolution. Overall change in hematoma thickness, midline shift and volume after 2 weeks of dexamethasone treatment was -3 mm (SD 7), -2 mm (SD 4) and -14 mL (SD 45) respectively (table 4). The homogeneous hypodense density subtype showed the largest decrease of radiological parameters compared to other subtypes (B-H), with mean changes in hematoma thickness, midline shift and volume after dexamethasone treatment of -7 mm (SD 3), -4 mm (SD 3) and -30 mL (SD 38) respectively (table 4; figure 3).

Multivariable linear regression analysis revealed a significant group effect for change in hematoma thickness between the 4 hematoma density groups (E-H). A larger decrease was observed in homogeneous hypodense hematoma compared to homogeneous hyperdense (adj. b -5.5 mm, 95% CI -9.0 to -2.1), mixed density (adj. b -4.5 mm, 95% CI -7.5 to -1.5) and homogeneous iso-dense hematoma (adj. b -3.8 mm, 95% CI -7.0 to -0.5). The combined density analysis also showed a significantly larger decrease in hematoma thickness in hematoma without hyperdense components (subtypes E and F) compared to hematoma with hyperdense components (subtypes G and H; adj. b -2.2 mm, 95% CI -4.1 to -0.3). No significant group effect for change in hematoma thickness was found between the hematoma architecture subgroups (A-D; p=0.53).

A significant group effect for change in midline shift was found in the combined density analysis with a larger decrease of midline shift in hematoma without hyperdense components (subtypes E and F) compared to hematoma with hyperdense components (subtypes G and H; adj. b -1.3 mm, 95% CI -2.7 to 0.0). No significant group differences were found between the individual density and architectural (A-H) subtypes for change in midline shift (p=0.1 and p=0.9 respectively), nor for change in hematoma volume in the architectural (A-D; p=0.2), density (E-H; p=0.6) or combined density (p=0.5) group analyses.

Clinical course

In 47 patients (55%) an improvement in neurological function was observed at primary follow- up evaluation, with a median onset of improvement on day 2 (IQR 1-4), corresponding to a daily dexamethasone dose of 16 mg (table 3). Multivariable linear regression analysis revealed a larger decrease in hematoma thickness (b -4.0, 95% CI -5.6 to -2.4), midline shift (b -3.1, 95% CI -4.1 to -2.0) and hematoma volume (b -33.5, 95% CI -49.9 to -17.0) in patient with neurological improvement compared to patients without neurological

Table 4. Radiological hematoma evolution – baseline versus follow up (two weeks)

Radiological parameter	CSDH (n=114)
Thickness (at two weeks)	
Overall – mm, mean (SD)	18 (8)
Change (mm) per density type	
Homogeneous hypodense, mean (SD)	-7 (3)
Homogeneous isodense, mean (SD)	-4 (4)
Homogeneous hyperdense, mean (SD)	-4 (15)
Mixed density, mean (SD)	-2 (4)
Change (mm) per architecture type	
Homogeneous (total), mean (SD)	-4 (9)
Laminar, mean (SD)	-3 (3)
Separated, mean (SD)	-2 (4)
Trabecular, mean (SD)	-2 (4)
Midline shift (at two weeks)	
Overall – present, n/n total (%)	83/85 (98)
Overall – mm, mean (+/- SD)	7 (4)
Change (mm) per density type	
Homogeneous hypodense, mean (SD)	-4 (3)
Homogeneous isodense, mean (SD)	-2 (4)
Homogeneous hyperdense, mean (SD)	-1 (3)
Mixed density, mean (SD)	-1 (5)
Change (mm) per architecture type	
Homogeneous (total), mean (SD)	-2 (3)
Laminar, mean (SD)	-1 (4)
Separated, mean (SD)	-1 (4)
Trabecular, mean (SD)	-1 (5)
Volume (at two weeks)	
Overall – mL, mean (SD)	106 (67)
Change (mL) per density type	
Homogeneous hypodense, mean (SD)	-30 (38)
Homogeneous isodense, mean (SD)	-16 (29)
Homogeneous hyperdense, mean (SD)	-4 (50)
Mixed density, mean (SD)	-14 (50)
Change (mL) per architecture type	
Homogeneous (total), mean (SD)	-15 (40)
Laminar, mean (SD)	2 (55)
Separated, mean (SD)	-28 (48)
Trabecular, mean (SD)	-9 (49)

improvement. Logistic regression analysis in the density subtypes (E-H) revealed homogeneous hyperdense hematoma to be a significant prognostic factor of no neurological improvement (odds ratio [OR] 0.08, 95% CI 0.0 to 0.8) compared to homogeneous hypodense hematoma. No significant group differences in neurological improvement were found in the architecture or combined density type analysis (p=0.8 and p=0.1 respectively).

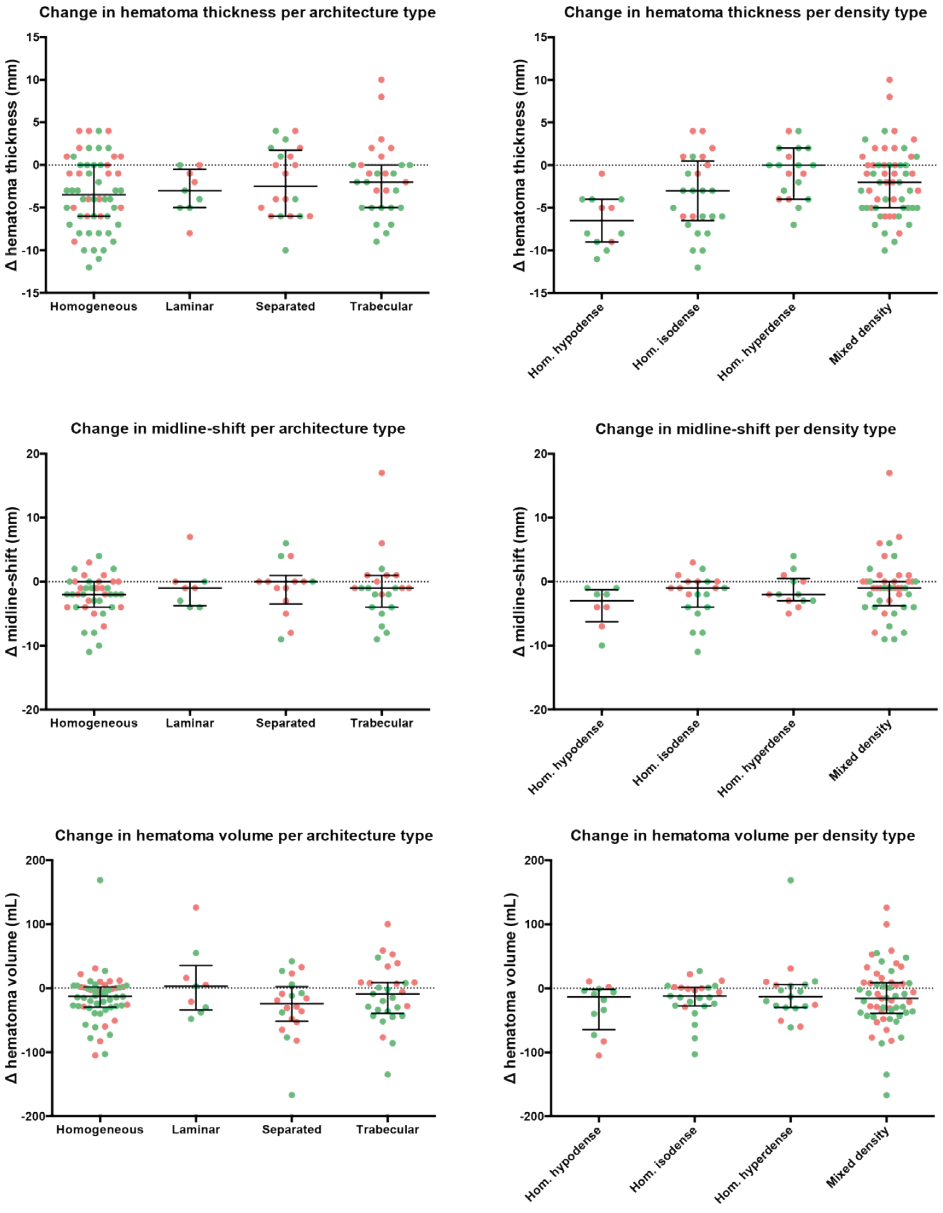

Figure 3. Boxplot of change in radiological parameter per hematoma subtype. Green dot: successful on dexamethasone monotherapy; Red dot: additional surgery required.

An improvement in Markwalder Grading Scale score at the primary follow-up evaluation was reported in 32 out of 85 patients (38%) with unchanged and deteriorated scores in 45 (53%) and 8 (9%) patients respectively (table 3,

figure 4). Improvement rates were higher in patients with hematoma without hyperdense components (subtype E-F; 52%) compared to hematoma with hyperdense components (subtype G-H; 31%). Lowest improvement rates were observed in patients with separated (10%) and homogeneous hyperdense hematoma (19%). No significant group differences in Markwalder Grading Scale score were found in the hematoma subtype (A-H) analyses. Functional independence (modified Rankin Scale score 0-2) was achieved in 35 (41%) patients after two weeks dexamethasone therapy (figure 5).

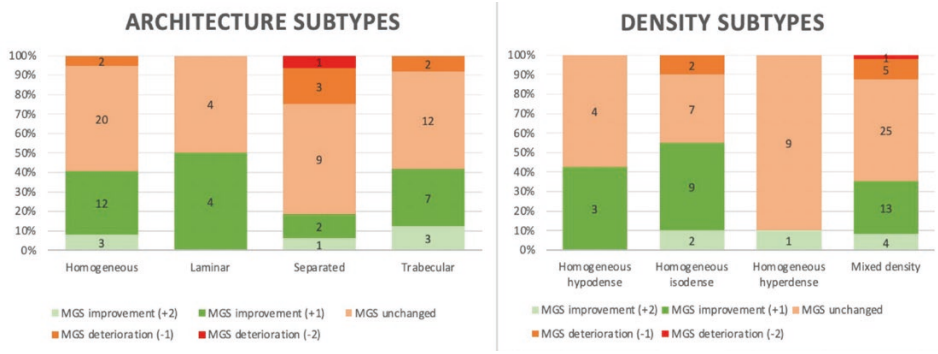

Figure 4. Change in symptom severity by hematoma subtypes – at two weeks. MGS = Markwalder Grading Scale score. Numbers in chart indicate total number of patients with specific change in MGS-score (improvement, no change, deterioration).

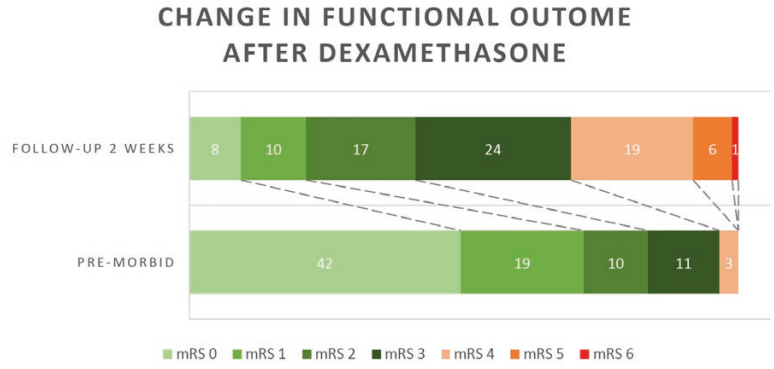

Figure 5. Change in functional outcome (modified Rankin Scale) – at two weeks. mRS = modified Rankin Scale score. Numbers indicate total number of patients with specific mRS-score.

Additional surgery

Decision to perform additional surgery at the primary follow up evaluation, was made in 48 patients (57%) with a median duration to surgery of 16 days (range 1-71; IQR 8-28; table 3). Clinical deterioration and unchanged radiological appearance were the main reasons to discontinue dexamethasone therapy, occurring in 32 (67%) and 21 (44%) out of 48 surgically treated patients, respectively. The need for surgery was highest in separated hematoma type, observed in 13 (80%) patients (figure 6).

Discussion

The present study showed the largest reduction in midline shift and hematoma thickness in chronic subdural hematoma without hyperdense components, after dexamethasone treatment in symptomatic patients. Additional surgery was performed in 57% of patients, with the highest observed rate (80%) in separated hematoma. This subtype, together with homogeneous hyperdense hematoma, showed the lowest rate of clinical improvement.

Our results show a difference in radiological response in the different chronic subdural hematoma subtypes after dexamethasone therapy. Four previous studies have reported on (overall) radiological response in relation to clinical outcome or chronic subdural hematoma recurrence after dexamethasone treatment for symptomatic chronic subdural hematoma [12,13,15]. These studies did not differentiate the response in specific chronic subdural hematoma

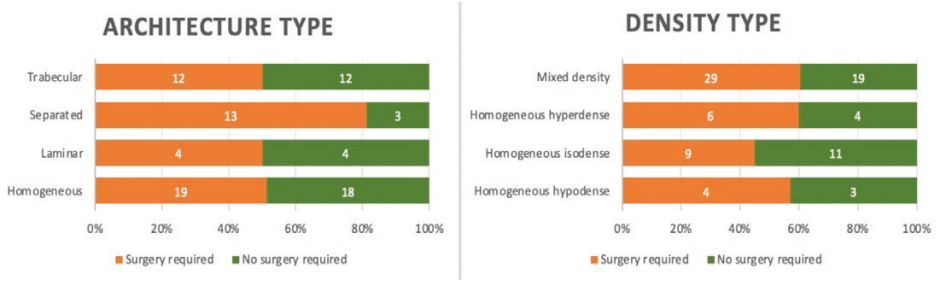

Figure 6. Need for additional surgery after dexamethasone therapy – by hematoma subtypes. Numbers indicate total number of patients requiring surgery (orange) or succeeded without surgery (green).

(density or architecture) subtypes. Smaller midline shift and hematoma thickness, as well as lower attenuation measurements in Houndsfield Unit (HU) – values than the pre-specified cut-off value at diagnosis, were suggested to favor beneficial effects of dexamethasone on clinical outcome or chronic subdural hematoma recurrence risk. The finding that low density hematoma respond more favorably to dexamethasone therapy, is consistent with our results that show the largest reduction in hematoma thickness and midline shift in hematoma without hyperdense components. This decrease in hematoma size is also reflected by a larger mean reduction in hematoma volume in hematoma without hyperdense components, although not reaching statistical significance. This is probably a methodological power issue, as a previous report demonstrated that midline shift in chronic subdural hematoma is associated with volume reduction [35].

The observed midline shift reduction in hematoma without hyperdense components after dexamethasone therapy underlines a decrease of hematoma pressure on brain parenchyma, favoring clinical improvement. Overall, we have demonstrated that greater reduction in hematoma size is associated with clinical improvement. Accordingly, higher rates of improvement in symptom severity expressed by the Markwalder Grading Scale score was observed in patients with hematoma without hyperdense components (52%) compared to hematoma with hyperdense components (31%). Because more subtle clinical improvements are likely to be missed by the five simplified categories of the Markwalder Grading Scale and the small subgroups in our data set, statistical significance in neurological improvement might have been missed.

At the initial homogeneous stage of chronic subdural hematoma development an inner and outer membrane mature around the subdural space [10,27,36]. Possibly, a balance is maintained during this homogeneous phase between the inflammatory cascade induced by hematoma degradation products, coagulation and fibrinolysis [25,37-38]. Recurrent hemorrhages, most likely triggered by head motion, have the opportunity to homogenize with the subdural collection. The anti-inflammatory effect of dexamethasone is presumably most effective at this phase because this stage encompasses the onset of inflammation in a steady-state [37,40,41]. In the subsequent two phases, defined as laminar followed by a separated hematoma, vascularity increases by formation of neo-capillaries and neo-membranes which are vulnerable structures prone to rupture, resulting in hematoma growth and progression of the inflammatory response [10,42,43]. An increase in fibrinolytic activity also contributes to

further hematoma enlargement in this phase. Chronic subdural hematoma recurrence rates have been reported highest during these hyper-fibrinolytic stages [10,29,37]. This underlying pathophysiology might explain why our fixed dexamethasone regimen was less effective in hematoma reduction in hematoma with hyperdense components compared to hematoma without. Dexamethasone might be insufficient in its inhibitory action on inflammatory and fibrinolytic mediators once the stage of separated hematoma is reached [17,38,43]. Accordingly, we observed higher rates of additional surgical treatment in separated type hematoma compared to other hematoma subtypes.

The identification of a radiological chronic subdural hematoma phenotype most responsive to dexamethasone therapy is important to assess whether there is any place for dexamethasone in the treatment algorithm of symptomatic chronic subdural hematoma. To identify these subgroups further research is necessary. Recent randomized trials showed a poorer effect of dexamethasone therapy combined with surgery as well as standalone therapy compared to surgery alone on achieving a good functional outcome (IP Miah, Dexamethasone versus surgery for chronic subdural hematoma, DECSA-trial: a randomized controlled trial, 2022, in submission) [29,30]. Overall, we found 41% of patients to achieve functional independence (modified Rankin Scale score 0-2) after two weeks dexamethasone. This necessitated additional surgery in the majority of patients. It is therefore likely that further research with dexamethasone in chronic subdural hematoma will become scarce. It is important to notice that current trials applied dexamethasone in the general population of symptomatic (Markwalder Grading Scale scores 1-3) chronic subdural hematoma patients including all hematoma subtypes. Whether treatment effects differ in specific radiological subtypes and mild symptomatic patients (Markwalder Grading Scale score 1), remains unknown. With the knowledge of the expected (extent of) radiological change per hematoma subtype, treatment effects might be optimized and better estimated by an improved patient selection.

A limitation of this study was the absence of a placebo-arm to confirm the treatment effect of dexamethasone. But maintaining a placebo-arm in symptomatic chronic subdural hematoma patients (Markwalder Grading Scale score 1-2) during 14 days to explore the radiological effect was deemed unethical. Since the aim of this substudy was to evaluate (short-term) radiological change in different chronic subdural hematoma – subtypes and the vast majority of patients showed slowly progressive symptomatology in weeks prior to diagnosis, it is likely that the observed improvement within the first

(mainly 2) days to two weeks, is due to dexamethasone effect rather than the natural disease course. Furthermore, the relatively small subgroups combined with the limited symptom severity classification by the Markwalder Grading Scale score, probably impaired the demonstration of significant differences in clinical improvement.

Conclusion

In this prospective substudy we found hematoma without hyperdense components to be most responsive to dexamethasone therapy in the reduction of hematoma size. The need for additional surgery was highest in patients with separated hematoma and this subtype, together with homogeneous hyperdense hematoma, showed lower rates of clinical improvement compared to other hematoma subtypes. The presence of hyperdense components in chronic subdural hematoma could therefore be of prognostic value for poor response to dexamethasone treatment. To explore whether dexamethasone has potential in specific patient groups, further research into the pathophysiology of chronic subdural hematoma, specific hematoma stages and subsequent radiological subtypes is warranted.

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