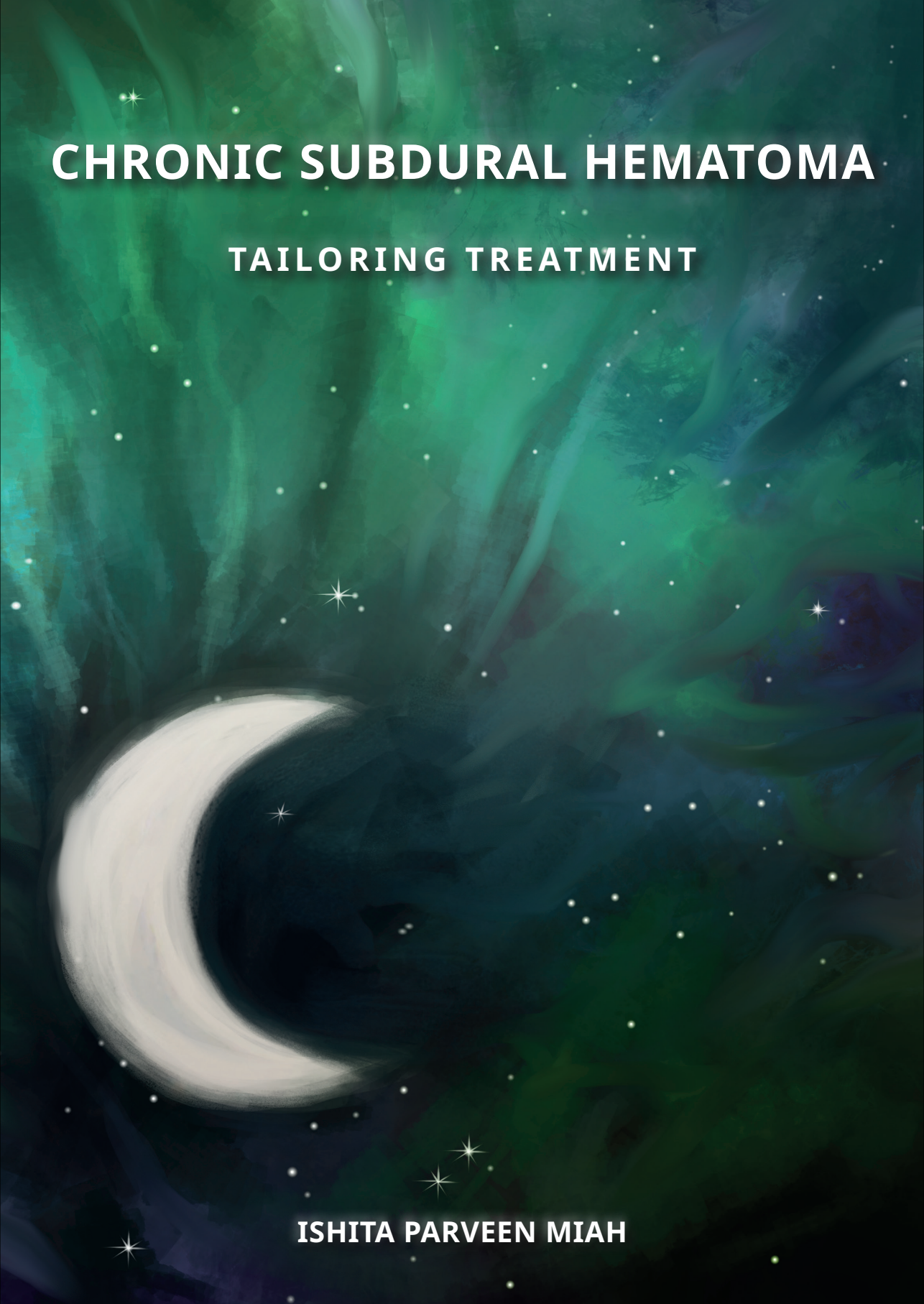
Chronic subdural hematoma: tailoring treatment

Miah, I.P.


CHRONIC SUBDURAL HEMATOMA
TAILORING TREATMENT
ISHITA PARVEEN MIAH

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Tailoring treatment

Ishita Parveen Miah

Chronic subdural hematoma - tailoring treatment
Ishita P. Miah

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Tailoring treatment

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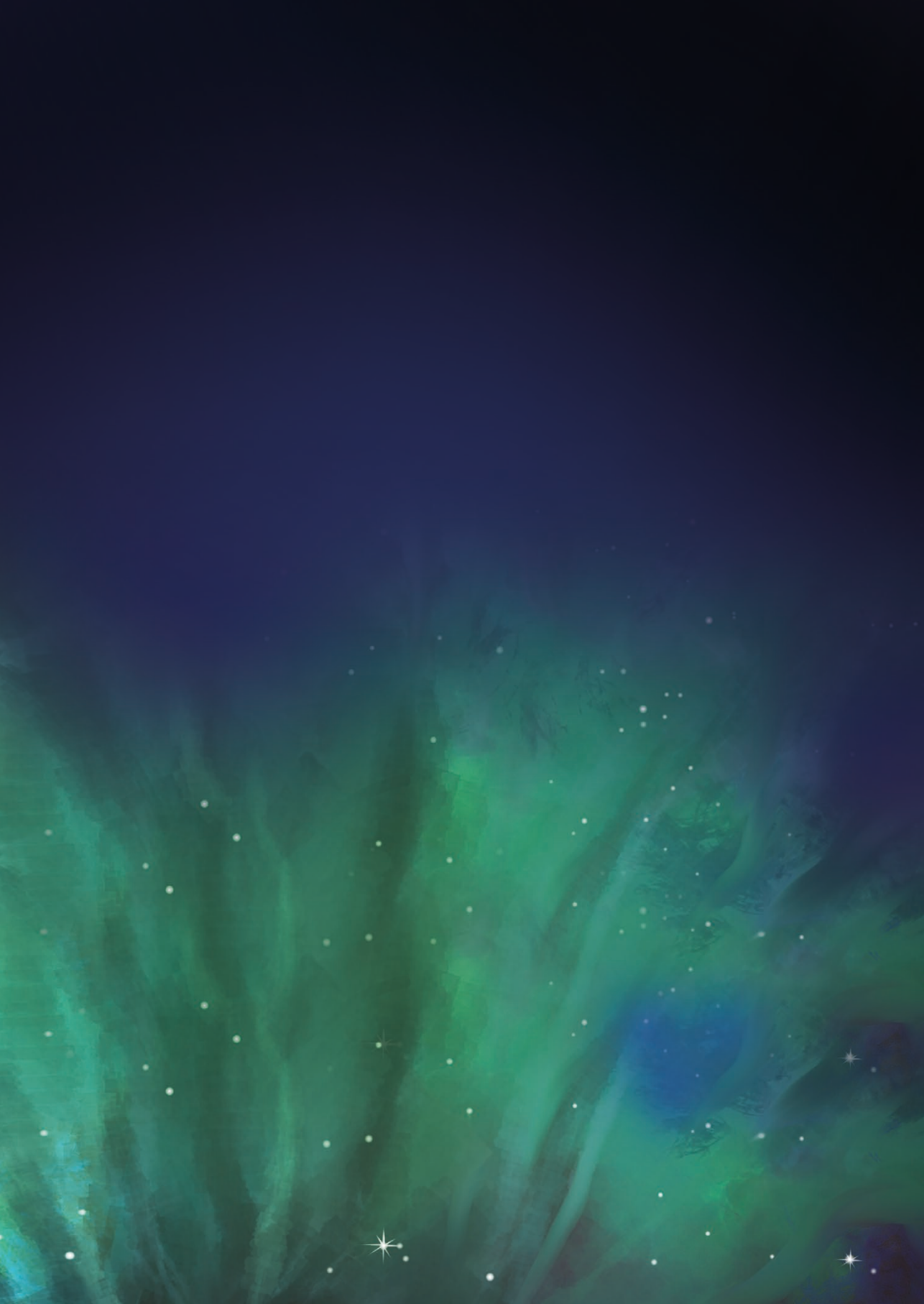

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Chronic subdural hematoma: a variable clinical picture asking for tailored treatment.

General introduction and outline of the thesis

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Epidemiology

A chronic subdural hematoma consists of an encapsulated collection of blood and blood degradation products in the subdural space, located between the outer two meninges of the brain, the arachnoid and dura mater (figure 1) [1]. Chronic subdural hematoma is a common neurologic disorder and a frequently occurring pathological entity requiring surgery in daily neurosurgical practice. An estimated 1-year incidence is 5-58/100.000 and highest among elderly with a mean age of 70-75 years [2-6]. The incidence is expected to increase due to the ageing population and the increasing use of anti-thrombotic therapy [7,8]. A chronic subdural hematoma is often preceded by a head trauma and predominantly affects males with an approximately 3:1 male to female ratio [9-10]. Bilateral chronic subdural hematoma occurrence is present in approximately 19% of cases [9,11].

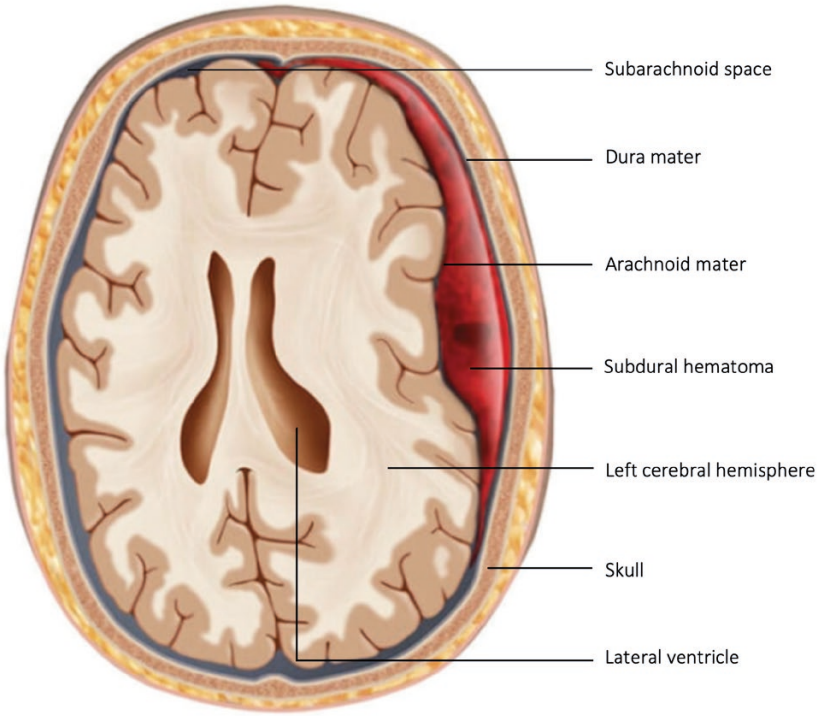

Figure 1. Chronic subdural hematoma

Diagnosis

The mainstay diagnostic modality for chronic subdural hematoma is computed tomography (CT). A chronic subdural hematoma appears as a mainly hypodense (< 30 Hounsfield units), isodense (30-40 Houndsfield units) or slightly hyperdense (40-50 Houndsfield units), crescent shaped fluid collection along the convexity [12-14]. Hyperdense components may be present, but compromise less than 1/3rd of the hematoma [figure 2]. There are still no (radiological) diagnostic criteria present for chronic subdural hematoma. An important radiological mimic of a chronic subdural hematoma is a subdural hygroma which consists of a subdural collection of cerebrospinal fluid, has the same density as cerebral spinal fluid (~0 Houndsfield units) and exerts no pressure on brain parenchyma [15]. Radiologically subdural hygroma can be indistinguishable from chronic subdural hematoma and the distinction remains a matter of debate. A density appearance higher than cerebrospinal fluid as well as mass effect on brain parenchyma, corresponds best with a chronic subdural hematoma. A second important radiological differential diagnosis is a subdural empyema consisting a suppurative collection which has a similar CT appearance to chronic subdural hematoma [16]. The distinction is best made with additional clinical information such as the presence of fever or a subfebrile condition after an upper airway infection (sinusitis, mastoiditis, otitis), trauma or cranial surgery.

Symptoms

Symptoms of chronic subdural hematoma are heterogeneous, and symptom onset and progression vary from days to weeks. Symptoms are most likely caused by the degree of compression of healthy brain parenchyma, and may range from no or transient symptoms, to headache, cognitive disturbances, (severe) focal neurological deficits or even coma [17]. To classify symptom severity the Markwalder Grading Scale score was developed in 1981 [18]. This scale consists of five ordinal categories ranging from no symptoms (Markwalder Grading Scale score 0) to a comatose condition (Markwalder Grading Scale score 4; table 1). The Markwalder Grading Scale score is mainly used for research purposes to indicate symptom severity of chronic subdural hematoma patients.

Table 1. Markwalder Grading Scale

Grade	Neurological symptoms
0	Patient neurological normal.
1	Patient alert and oriented; mild symptoms such as headache; absent of mild neurological deficit such as reflex asymmetry.
2	Patient drowsy (defined as Glasgow Coma Scale, GCS, score: 13-14) or disoriented with variable neurological deficit, such as hemiparesis.
3	Patient stuporous (defined as GCS 9 – 12) but responding appropriately to noxious stimuli; severe focal signs such as hemiplegia.
4	Patient comatose (GCS 8 or lower) with absent motor responses to painful stimuli.

Pathophysiology

Two possible pathophysiological pathways have been postulated for chronic subdural hematoma formation [19, 20]. The first pathway includes the formation of an acute subdural hematoma due to tearing of bridging veins traversing the brain from the dural venous system, causing an accumulation of venous blood within the subdural space. Over time, if hematoma absorption is insufficient, this acute subdural hematoma may develop into a hematoma of older age resulting in a chronic subdural hematoma. The second pathway of chronic subdural hematoma formation consists of an inflammatory response in the subdural space. The majority of patients developing a chronic subdural hematoma, initially show normal (cranial) imaging after a head trauma and roughly 40% of patients do not even experience a head trauma [21]. This patient category becomes symptomatic in several weeks, a time line which is much slower than the assumed venous hemorrhages which would accumulate within days and cause focal neurological symptoms on shorter notice. This subpopulation emphasizes the importance of the second pathway of chronic subdural hematoma – formation: a chronic inflammatory response in the dura mater [22].

Any form of injury (i.e., trauma, infection, cellular injury) can cause the lining cells of the dura to split from the subsequent layer of arachnoid barrier cells resulting in cerebral spinal fluid leakage. An inflammatory response is then incited to aid tissue repair, but in chronic subdural hematoma this reaction is sustained resulting in fibrin exudation by the dural border cells and formation of neomembranes and neocapillaries [23-28]. These structures produce high

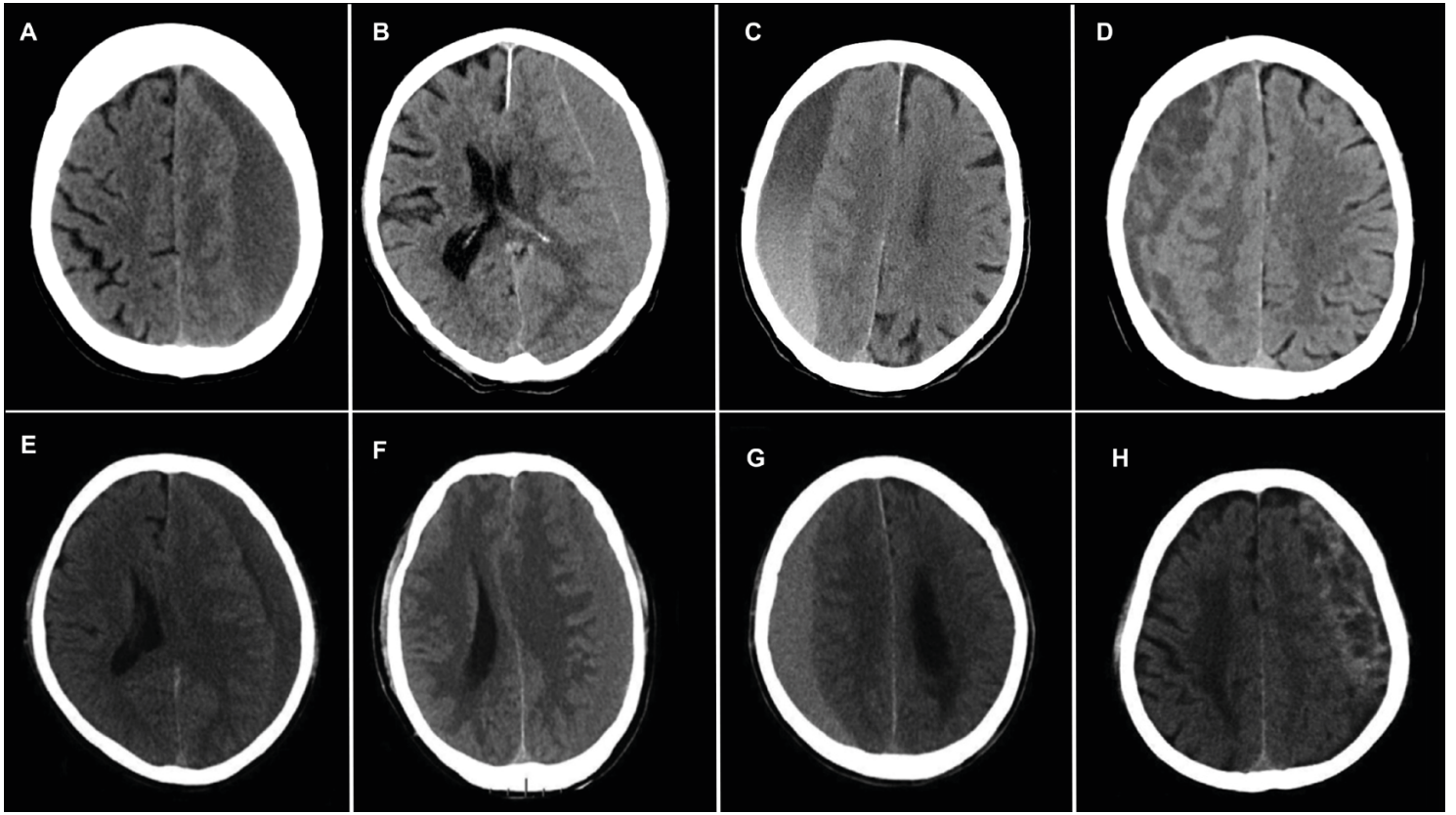

Figure 2. Radiological chronic subdural hematoma subtypes (A-D: achitecture types; E-H: density types). A. Homogeneous hematoma (hypodense type); B. Laminar hematoma; C. Separated hematoma; D. Trabecular hematoma; E. Homogeneous hypodense hematoma; F. Homogeneous isodense hematoma; G. Homogeneous hyperdense hematoma; H. Mixed density hematoma.

concentrations of several angiogenic factors of which vascular endothelial growth factor (VEGF) is one of the key factors, and are vulnerable for rupture resulting in further progression of the inflammatory response and hematoma enlargement. Inflammatory mediators also stimulate vascular permeability and the release of tissue plasminogen activator (t-PA) as well as thrombomodulin from endothelial cells, causing an increase in fibrinolytic activity by activation of plasminogen and further contributing to hematoma increase [29-30]. This cascade of inflammation, angiogenesis and hyperfibrinolysis, is well illustrated by a chronic subdural hematoma – cycle that is responsible for hematoma maintenance and enlargement (figure 3).

Risk factors that are thought to contribute to the development of chronic subdural hematoma are advanced age, cerebral atrophy, (minor) head trauma, low intracranial pressure states and coagulopathies due to antithrombotic therapy or an underlying systemic disease [11, 31-37].

Treatment

To date no uniform treatment guideline exists. Treatment varies from observation only in asymptomatic or mildly affected patients, to pharmacological or surgical

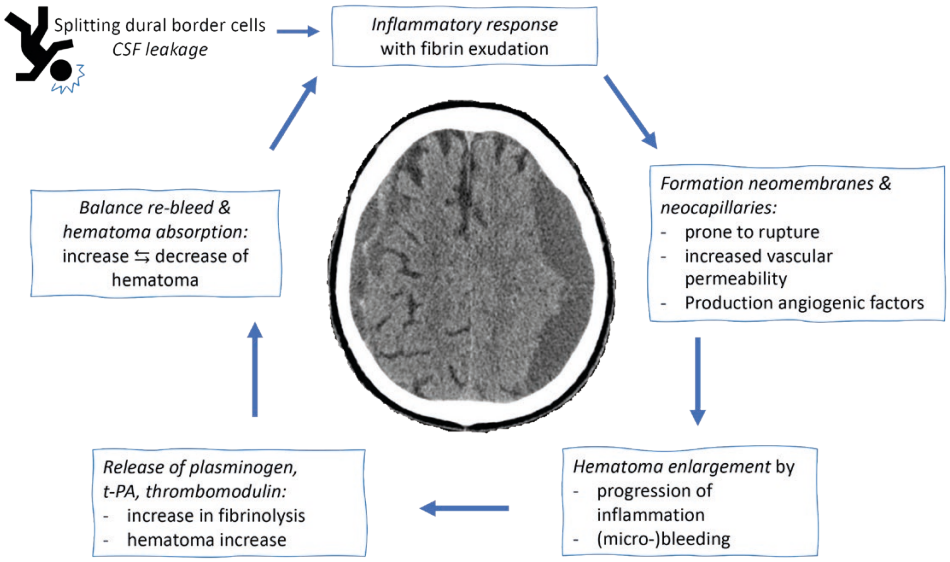

Figure 3. Pathophysiology chronic subdural hematoma – inflammatory cycle

treatment in symptomatic patients, with primary surgery in case of severe symptoms [17]. This results in a wide variation in clinical practice worldwide. Surgery is still the mainstay treatment and expected to become one of the most common performed neurosurgical procedures in 2030 due to the rise in chronic subdural hematoma incidence [38]. The main surgical procedure consists of a twist-drill or burr hole craniostomy, with either general or local anesthetics. One or two burr-holes are drilled in the maximum width of the hematoma depending on the hematoma configuration. The use of a closed system drainage after burr hole evacuation during 24-48 hours reduces the rate of chronic subdural hematoma recurrences significantly by half [9, 39]. Despite optimizing surgical techniques, surgery is still associated with complications (i.e., wound infections, hemorrhages in surgical trajectory) in 1-16%, recurrences up to 30% and mortality of 3-32% [9, 39-43]. The establishment of an optimal treatment strategy for chronic subdural hematoma is therefore an important focus of attention.

Pharmacological agents

Although surgery is the main treatment in symptomatic patients, a conservative (pharmacological) approach seems an interesting alternative or add-on to surgery to optimize clinical outcome in this elderly and vulnerable patient population. To counteract the above mentioned chronic subdural hematoma cycle, several pharmacological agents have been reported as an alternative therapy by their inhibitory actions on inflammation, angiogenesis and hyperfibrinolysis (table 2).

As shown in table 2, most studies are performed with corticosteroids as a conservative treatment modality in chronic subdural hematoma. In the following paragraph, the evidence of corticosteroids as monotherapy, that led to the initiation of the studies in this thesis, will be evaluated in more detail.

Corticosteroids

The most widely used pharmacological agent in chronic subdural hematoma are corticosteroids and in particular dexamethasone. Dexamethasone is a synthetic version of an endogenous steroid hormone with strong anti-inflammatory properties by inhibition of pro-inflammatory transcription

Table 2. Overview of pharmacological agents in chronic subdural hematoma treatment

Type of agent	Mechanism of action	Author and year	Study design	No. of patients	Treatment	Primary outcome	In favor of drug
Angiotensin converting enzyme – inhibitors	Mediation of angiogenesis (inhibition VEGF)	Weigel et al. 2007 [44]	Retro.	438	ACE+S, S	reCSDH	yes
		Poulsen et al. 2014 [45]	RCT	47	ACE+S, S	reCSDH	no
		Neidert et al. 2015 [46]	Retro.	203	ACE+S, S	reCSDH	no
		Bartek et al. 2018* [47]	Retro.	1252	ACE+S, S	reCSDH	no
Corticosteroids	Inhibition inflammatory factors, decrease of vascular endothelial permeability	Bender et al. 1974 [48]	Retro.	185	C, CS, S	Recovery	yes
		Pichert et al. 1987 [49]	Retro.	66	C, CS, S	Recovery	yes
		Sun et al. 2005 [50]	Pros.	112	C, CS, S	FO (GOS)	yes
		Dran et al. 2007 [51]	Retro.	198	CS, S	Survival	yes
		Delgado-Lopez et al. 2009 [52]	Retro.	122	C, CS, S	FO (MGS)	yes
		Berhauser Pont et al. 2012 [53]	Retro.	496	CS	reCSDH	yes
		Chan et al. 2015 [54]	Pros.	248	CS, S	reCSDH	yes
		Thotakura et al. 2015 [55]	Pros.	26	C, CS	Recovery	yes
		Prud'homme et al. 2016 [56]	RCT	20	C (+S), P (+S)	No surgery	no
		Qian et al. 2017* [35]	Retro.	242	CS, S	reCSDH	yes
		Fountas et al. 2019* [57]	Retro.	171	C, CS, S	reCSDH	yes
		Mebberson et al. 2020* [58]	RCT	47	C (+S), P (+S)	reCSDH	yes
		Hutchinson et al. 2020* [59]	RCT	748	C (+S), P (+S)	FO (mRS)	no

Statins	Anti-angiogenic, anti-inflammatory, fibrinogenic effects	Wang et al. 2014 [60]	Pros.	23	St.	CSDH volume	yes
		Liu et al. 2016 [61]	Pros.	80	St. (+S), P (+S)	No surgery	yes
		Min et al. 2016 [62]	Retro.	109	St, St+S, S	CSDH volume	yes
		Xu et al. 2016 [63]	Retro.	109	St, St+S, S	CSDH volume	yes
		Jiang et al. 2018 [64]	RCT	196	St. (+S), P (+S)	CSDH volume	yes
		Tang et al. 2018 [65]	Retro.	245	St+S, S	reCSDH	yes
Tranexaminic acid	Anti-fibrinolytic effects	Kageyama et al. 2013 [66]	Retro.	18	TXA, TXA+S	CSDH volume	yes
		Tanweer et al. 2016 [67]	Retro.	14	TXA+S	CSDH volume	yes
		Yamada et al. 2020 [68]	RCT	72	S, S+TXA, S+G	reCSDH	no
		Kutty et al. 2020 [69]	Pros.	24	TXA	Recovery	yes

*Publication of study after initiation of PhD – trajectory (>2016) and will be discussed in discussion – section; ACE = angiotensing converting enzyme inhibitor; C = corticosteroid; CS = corticosteroid combined with surgery; CSDH = chronic subdural hematoma; FO = functional outcome; G = goreisan; GOS = Glasgow outcome scale; MGS = Markwalder grading scale; mRS = modified Rankin Scale; P = placebo; Pros. = prospective; RCT = randomized controlled trial; reCSDH = recurrent chronic subdural hematoma; Retro. = retrospective; S = surgery; (+S) = additional surgery if conservative management insufficient; St.= statin; TXA = tranexaminic acid.

factors [70]. One of its applications in neurological patients has been in the reduction of cerebral oedema secondary to structural intracranial lesions such as neoplasia [71]. In addition to the anti-inflammatory effects, corticosteroids are capable of preservation of vascular endothelial barrier integrity. Through upregulation of several endothelial junctional proteins and down-regulation of specific enzymes responsible for junctional protein cleavage, a reduction in vascular permeability is established and hence fluid accumulation around i.e. brain tumors [70]. The postulated effect of dexamethasone in chronic subdural hematoma therefore might be caused by a dual mechanism through inhibition of the inflammatory response in the subdural space and prevention of fluid exudation and bleeding from premature vessels seen in neomembranes.

What do we (not) know

The use of corticosteroids in chronic subdural hematoma as monotherapy was first described in 1974 by Bender [48]. In this study 185 symptomatic patients received primary surgical or different forms of conservative (medical) therapy. In total 27, mainly mildly symptomatic patients, received corticosteroid monotherapy with prednisolone 60 mg daily or an equivalent dose of dexamethasone during 21 days, and reached good clinical recovery. The authors conclude chronic subdural hematoma may spontaneously resolve and hematoma resolution might be facilitated with steroids, which seems a safe option in mildly symptomatic patients. A second cohort study of 66 symptomatic chronic subdural hematoma patients was published in 1987 [49]. In this study, the majority was treated with monotherapy dexamethasone (46/66), seven patients were treated with dexamethasone combined with surgery and thirteen with surgery alone. Steroid-treated patients received 16 mg of dexamethasone daily, which was slowly tapered with a treatment duration of 8 weeks. In total 83% of patients treated with dexamethasone monotherapy were symptom-free and the authors postulate corticosteroid treatment can be recommended if strict guidelines are observed. A few years later two additional cohort studies were published in 2005 and 2009. These studies reported on clinical outcome in 112 and 122 patients after either surgery alone, post-operative dexamethasone, dexamethasone monotherapy, or initial dexamethasone with additional surgery [50, 52]. In the first study dexamethasone was dosed 16 mg daily during 21 days and in the second study 12 mg daily during three days, tapered by 1 mg a day. A favorable functional outcome, expressed by a Glasgow Outcome Scale score (GOS) of 4-5 or Markwalder Grading Scale score 0-2, was reported in 84% at

six months and 96% at six weeks in the dexamethasone – group respectively. In the surgical group however, favorable outcome was reported in 75-93% of patients. Based on these results, the authors recommended dexamethasone therapy as a conservative alternative treatment strategy in selected patients. In 2015 a cohort study was performed in 26 symptomatic patients with chronic subdural hematoma [55]. All patients received initial dexamethasone therapy in a dosing scheme of 12 mg daily during three days, which was tapered in four weeks, combined with 30 mg prednisolone daily which was tapered in three weeks. In total 42% achieved complete recovery with steroid monotherapy, with the remaining 58% requiring additional surgery. After analyzing the dexamethasone-success group, the authors conclude patients with low grade chronic subdural hematoma (lesser hematoma thickness and midline shift) can be successfully treated by dexamethasone. Finally, in 2016 the results of a first randomized pilot study were published in which ten patients received dexamethasone and ten placebo treatment. Dexamethasone was administered in a daily dose of 12 mg for three weeks followed by tapering. The success rate (no need for additional surgery) was 60% (6/10) in the dexamethasone group versus 70% (7/10) in the placebo group. The complication rate however was significantly higher after dexamethasone therapy. The authors conclude no beneficial effect of dexamethasone compared to placebo.

Variation in clinical practice

Based on these data and expert-opinion, dexamethasone has been applied as an alternative or adjuvant to surgery for chronic subdural hematoma treatment. The following two cases illustrate the treatment variation in daily clinical practice and observed treatment effect of both surgery and conservative therapy with dexamethasone.

Patient A, a 69-year-old man, was referred to the emergency department by his general practitioner because of a gradually progressive headache and memory complaints. The patient hit his head against an air conditioner while he was on holiday four weeks earlier. Since then, he experienced a nagging pain in the forehead. The symptoms progressed and since the last week he felt slower in his movements and thinking, had problems articulating and he also experienced weakness in the left arm and leg. Due to these symptoms, he was no longer able to perform his work as a manager in the healthcare sector.

The patient had a history of hypertension, hypercholesterolemia and atherosclerosis. He used carbasalate calcium 100 mg once daily as cardiovascular risk management.

On neurological examination we noticed an impaired articulation and a left-sided hemiparesis. In view of the previous trauma and the gradually progressive symptoms, we suspected a chronic subdural hematoma. A cranial CT scan revealed a subdural hematoma with a maximum hematoma thickness of 14 mm, with compression on the right hemisphere and displacement of brain structures across the midline to the left (figure 4). We stopped his carbasalate calcium and admitted the patient because of the progressive, debilitating symptoms. The patient was treated the next day with a burr hole craniostomy with subdural drainage. Immediately after the operation, the strength in his left arm and left leg improved, his headache was considerably less and the patient was able to walk independently without aids. The second day after the operation, we removed the subdural drain and the patient was discharged home the same afternoon. We resumed the carbasalate calcium therapy the next day.

At the outpatient clinic three months after the operation, his symptoms were resolved except for the occasionally occurring problems maintaining his balance. He was able to resume his work, fitness and travelling again.

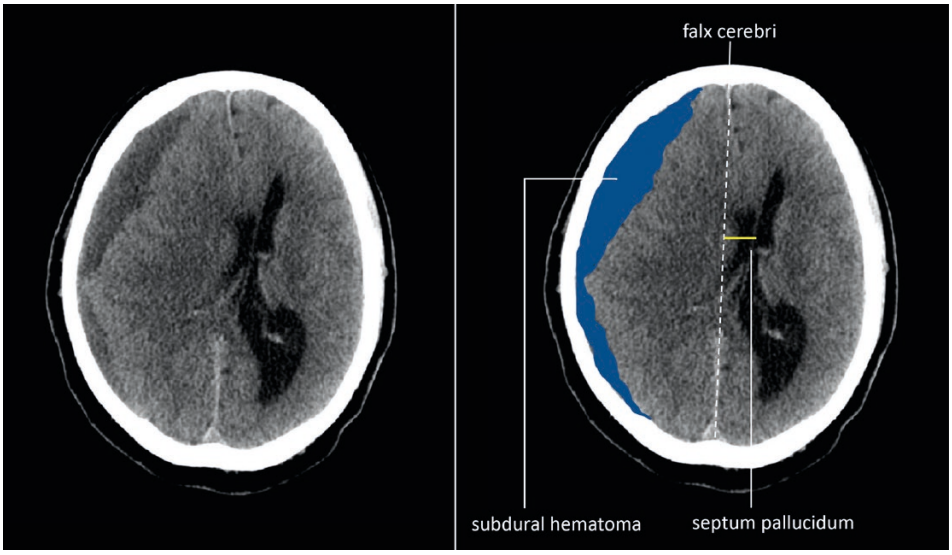

Figure 4. Patient A - CT scan of chronic subdural hematoma at presentation

Patient B, a 75-year-old man, visited the general practitioner because of increasing headaches with persisting nausea and vomiting for a week. He had fallen with his head against a heater during the night three weeks earlier. Since the past 24 hours, he experienced a slurred speech and his walking deteriorated, causing him to fall frequently. Since the first fall, the patient also experienced more difficulties with his memory. According to his wife, his statements were not always correct. The patient had a history of atrial fibrillation for which he used a vitamin K antagonist (acenocoumarol). The general practitioner suspected a neurodegenerative disorder because of the memory problems and the tendency to fall, but in view of the progression he also took an intracranial hemorrhage or tumor into account. He referred the patient to the emergency department. During the neurological examination, we noticed a slurred speech and an unstable gait due to weakness of the left leg. We suspected a chronic subdural hematoma given the head trauma and the use of an oral anticoagulant. A cranial CT showed a subdural hematoma over the right convexity with a maximum hematoma thickness of 21 mm and displacement of the brain structures along the midline to the left (figure 5a). The measured international normalized ratio (INR) value was 3.4. We ceased his anticoagulant therapy, administered prothrombin complex concentrate as an antidote for the vitamin K antagonist and admitted the patient to the ward. Because of the minimal paresis of the left leg, we treated him with dexamethasone 8 mg twice daily for four days, after which we lowered the dose by halve every three days. On the second day of dexamethasone therapy, he clearly experienced an improvement of his headache and his gait and speech gradually improved during the following days. On day six of admission, the patient was discharged home in good condition.

He continued physical therapy at home and completed his 19-days dexamethasone tapering scheme. At the outpatient clinic 2 weeks after admission, the headache had disappeared and he continued to experience further improvement of his gait and balance.

A follow-up cranial CT showed a decrease in hematoma thickness and midline shift (figure 5b). Based on the clinical and radiological improvement, we decided to resume his anticoagulant therapy. During his second follow up at the outpatient clinic three months later, the patient had recovered well and he had recently been on vacation. Besides the residual complaints of fatigue and memory, he did not experience any other impairments in daily living.

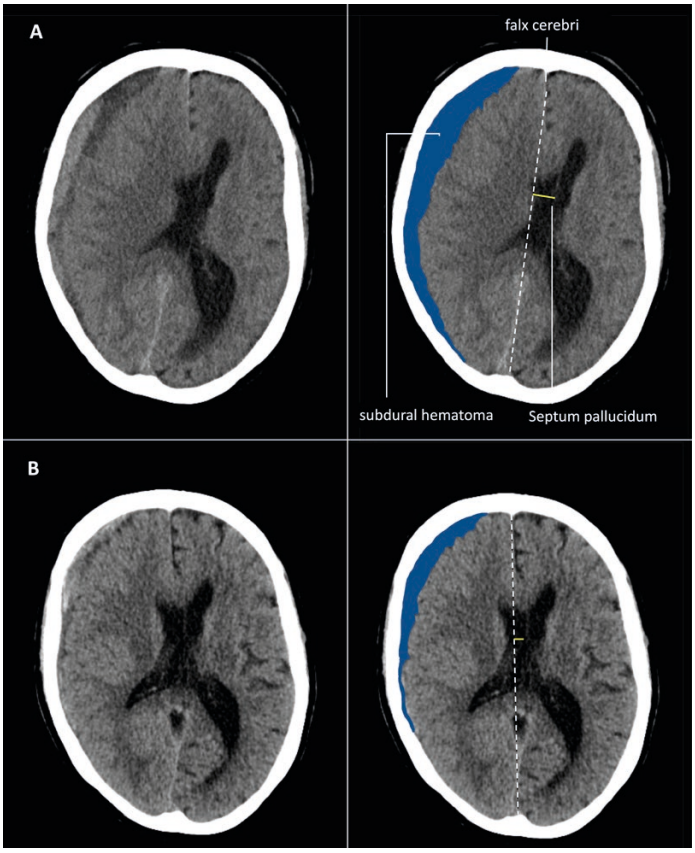

Figure 5. Patient B – CT-scan of chronic subdural hematoma at presentation (A), follow-up (B)

Both case reports describe symptomatic patients with similar symptom severity on the Markwalder grading scale (score 2), who achieved good recovery after two different treatment strategies. In patient A, surgery resulted in a quick improvement of symptoms. Although the improvement occurred more gradually with dexamethasone therapy in patient B, a favorable recovery was achieved preventing an operation. To date no head-to-head comparison has been made between dexamethasone therapy versus surgery in the treatment of symptomatic patients with chronic subdural hematoma. As a consequence, different treatment strategies are maintained between hospitals for symptomatic patients, without any clarity on the most effective and safest therapy. This emphasizes the necessity of high-quality studies and randomized controlled trials. Therefore, we designed and initiated the DECSA trial, a randomized controlled trial in which we compared the clinical effectiveness of dexamethasone compared to surgery in symptomatic chronic subdural hematoma patients.

Radiological hematoma characteristics

Chronic subdural hematoma appearance on CT varies from hypo- to slightly hyperdense relative to adjacent brain parenchyma [72]. The density reflects the age of the hematoma due to the evolution of the blood degradation products, with hypodense areas representing hematoma of older age and hyperdense components more recent or active bleeding [73-75]. An accepted and frequently used radiological classification system in clinical practice is based on hematoma density, categorizing four types of chronic subdural hematoma: homogeneous hypodense, -isodense, slightly hyperdense and mixed density hematoma (figure 2). A second classification has been proposed by Nakaguchi and is based on CT architecture types that 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 [76; figure 2]. In light of the inflammatory pathogenesis hypothesis and forementioned radiological subtypes reflecting a different hematoma age and stage of inflammation, response to treatment, and in specific corticosteroids, could be different in the various subtypes.

Many radiological (CT) parameters have been reported to be associated with treatment effect on chronic subdural hematoma recurrence risk or functional outcome [76-89]. A wide variety of parameters have been described to be of prognostic value, including hematoma laterality, preoperative hematoma thickness and midline shift, hematoma density and internal architecture types, cerebral atrophy and hematoma volume. Due to the heterogeneity in data and conflicting results, it is difficult to draw firm conclusions.

As with many neurological disease entities (i.e. neurovascular, -oncological or demyelination), radiological appearance is used to initiate an appropriate therapy which is expected to achieve the best possible functional outcome. It is therefore of importance that this principle is also pursued for optimal chronic subdural hematoma treatment, leading to tailored treatment measures accomplishing personalized medicine. We have therefore performed a systematic review and meta-analysis to explore the prognostic value of radiological parameters in chronic subdural hematoma after surgical treatment. Subsequently we have designed a prospective CT-study in dexamethasone treated patients to assess whether the short-term radiological as well as clinical response can be predicted by the baseline radiological hematoma appearance.

Outline of the thesis

In this thesis we evaluate the efficacy of dexamethasone therapy in symptomatic chronic subdural hematoma patients and explore the prognostic value of baseline radiological hematoma characteristics in predicting treatment effect.

We start off in **chapter 2** with a retrospective analysis of the efficacy of initial dexamethasone therapy versus primary surgery on functional outcome in two large Dutch neurosurgical centers, each with their own treatment protocol. This chapter will set the grounds for the large multicenter randomized clinical trial – DECSA –, that studies the effectiveness of initial dexamethasone therapy versus primary surgery in achieving good functional outcome.

Chapter 3 provides the protocol publication of the DECSA trial, explaining the choices that were made in designing the study. The results of the DECSA trial are then presented in **chapter 4**.

After having provided the context and evidence of dexamethasone therapy in symptomatic patients, we explore the prognostic value of radiological parameters for treatment effect in chronic subdural hematoma with a systematic review and meta-analysis of current literature in **chapter 5**.

Finally, in **chapter 6** the outcomes of this review are implemented in a prospective radiological sub-study in symptomatic chronic subdural hematoma patients all treated with dexamethasone, to evaluate which radiological hematoma subtype is most responsive to dexamethasone therapy.

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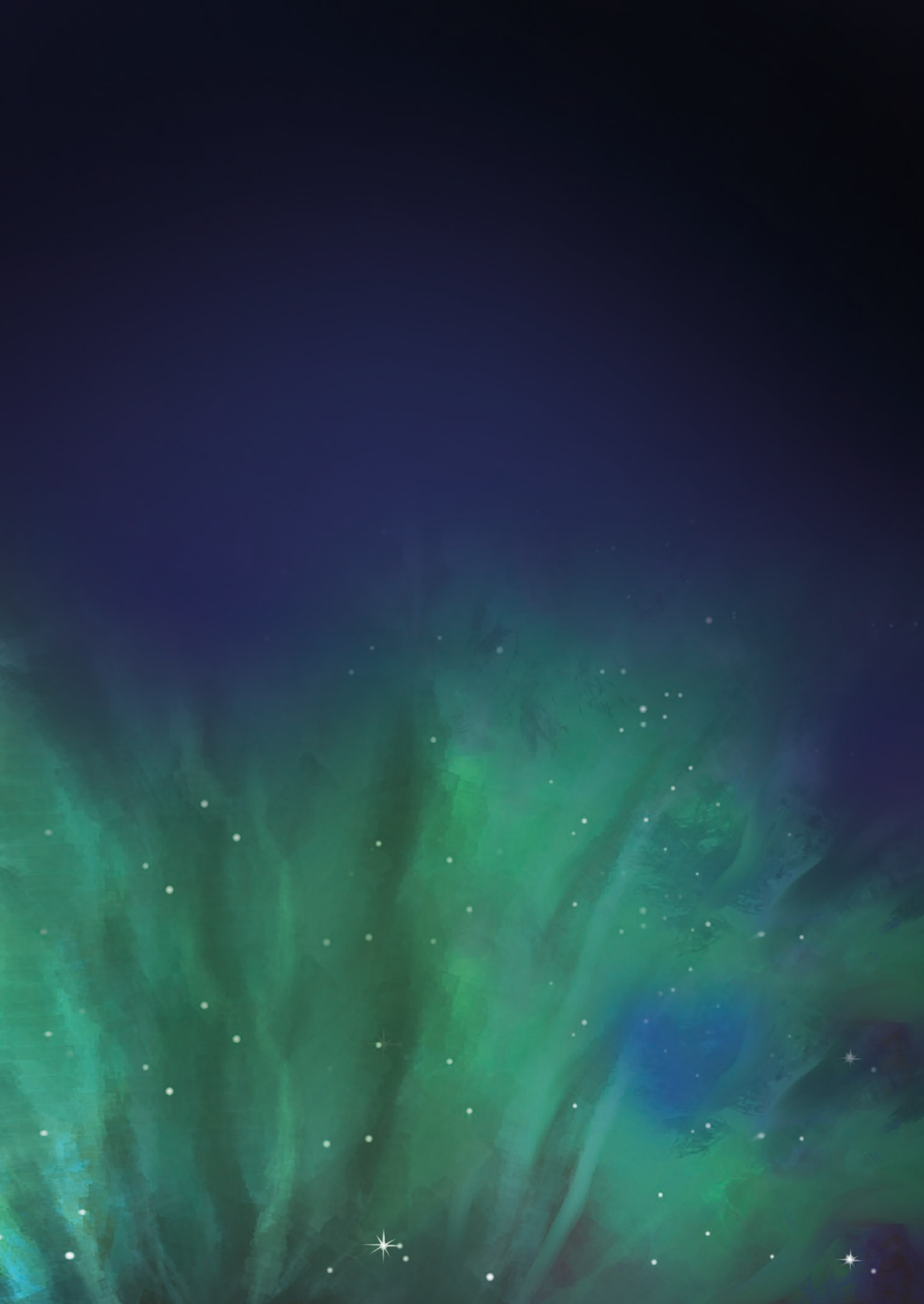

2

Dexamethasone Therapy in Symptomatic Chronic Subdural Hematoma (DECSA–R): A Retrospective Evaluation of Initial Corticosteroid Therapy versus Primary Surgery

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Abstract

Worldwide, different strategies are being applied for symptomatic chronic subdural hematoma (CSDH). The aim of this study was to evaluate the efficacy of two treatment strategies for symptomatic CSDH: initial dexamethasone (DXM) therapy versus primary surgery by burr hole craniostomy (BHC). We retrospectively collected data for 120 symptomatic CSDH patients in two neurotrauma centers between 2014 and 2016, each with their own treatment protocol. Sixty patients received primary BHC (center A), and another 60 initial DXM therapy (center B). Primary outcome was evaluated by dichotomized modified Rankin Scale (mRS) score (0–3 and 4–6) and Markwalder Grading Scale (MGS) score at three months. Secondary outcomes were additional interventions, CSDH recurrence, mortality, complications, and duration of hospital stay. Baseline characteristics were similar in both groups. At three months, a favorable mRS score (0–3) was observed in 70% and 76% of patients in cohort A and B, respectively (odds ratio [OR] 0.77, 95% CI 0.30–1.98; p=0.59). A favorable MGS score (0–1) was observed in 96% of patients in both groups (OR 0.98, 95% CI 0.45–2.15; p=0.95). CSDH recurrence was 12% in cohort A and 22% in cohort B (p=0.15). Mortality was 10% in both cohorts. In cohort B, additional surgery was performed in 83% at a median of six days, and significantly more patients had complications (55% vs. 35%, p = 0.02), a prolonged hospitalization (10 vs. 5 days; p = 0.02), and one or more follow-up cranial CT's (85% vs. 48%; p<0.001). To achieve a favorable clinical outcome, initial DXM therapy was associated with a high rate of crossover to surgery, significantly longer overall hospital stay, and more complications compared to primary surgery.

Introduction

Chronic subdural hematoma (CSDH) is a common neurological disease in the elderly population with a rapidly rising incidence due to increasing age and use of anticoagulant therapy [1,2]. Worldwide different treatment strategies are applied for symptomatic patients, which consists of primary surgery or corticosteroid therapy as monotherapy or adjuvant therapy prior to or after surgery [3]. The administration of different treatment modalities depends on expert opinion of the treating physician and scarce data from previous studies. To date, there is a lack of consensus regarding the optimal treatment strategy for symptomatic CSDH.

Surgery with subdural drainage is the mainstay treatment [4]. Due to relevant surgical complications, a recurrence risk up to 30% and increased mortality in this vulnerable patient population, corticosteroid therapy is being administered as an alternative or adjuvant treatment modality [3-7]. It has been postulated that corticosteroids have the capacity to block the anti-inflammatory changes in the formation of the hematoma and in particular impede the formation of neo-membranes and neo-capillaries by their powerful inhibition of inflammatory mediators [8-11].

Previous studies revealed possible beneficial effects of dexamethasone (DXM) therapy applied as monotherapy or adjuvant therapy, achieving an equal or slightly superior effect on clinical outcome compared to primary surgery alone [12-18]. Further, the administration and longer duration of DXM therapy as monotherapy or prior to surgery might also lower recurrence risk and mortality [16-19]. These results however must be interpreted with caution due to selection bias of patients and evident heterogeneity in the evaluated cohorts.

The aim of this study is to assess the effect of primary surgery by burr hole craniostomy (BHC) versus initial DXM therapy on clinical outcome in two equal retrospective cohorts of symptomatic CSDH patients. Furthermore, the effect of both treatment strategies on CSDH recurrence, complications, and duration of hospital stay is evaluated.

Methods

Overall study design

This retrospective study evaluates the effect of initial DXM therapy versus primary surgery by BHC in symptomatic CSDH patients. This comparison was made by collecting data of 120 consecutive patients in two large Dutch neurotrauma centers during the timeframe of inclusion, January 2014 to December 2016. Participating centers were Haaglanden Medical Center, The Hague (HMC, center A) and Elisabeth—TweeSteden Hospital, Tilburg (ETZ, center B), each applying a different treatment regimen for symptomatic CSDH patients. Primary surgery was performed in center A and initial DXM therapy was administered in center B.

Patient population

Patients were eligible for inclusion if they: 1) were at least 18 years of age; 2) presented with symptomatic CSDH, defined as an iso-dense or hypodense hematoma in the subdural space on cranial CT-scan (hyperdense components may be present but must com- promise less than 1/3 of the hematoma); 3) had a correlation of clinical symptoms to CSDH; and 4) had a symptom severity score 1 or 2 on the Markwalder Grading Scale (MGS) [20]. Exclusion criteria were: 1) acute subdural hematoma; 2) asymptomatic CSDH (MGS 0); and 3) severe symptoms due to CSDH with MGS score of 3 or 4 prompting emergency surgery. Asymptomatic patients (MGS 0) were excluded because this patient group received an approach with observation only in both hospitals.

Study treatment

The surgical procedure was identical in both hospitals and consisted of a burr hole craniostomy (BHC), with either general (center B) or local anesthetics (center A). One or two burr holes were drilled over the maximum width of the hematoma, depending on the hematoma configuration. After the subdural collection was washed out with Ringer's lactate saline at body temperature, a subdural drain was inserted for two days. In both hospitals, the moment of surgery depended on the clinical condition of the patient, use of anticoagulant agents or anti-platelet therapy and surgical capacity.

DXM treatment was administered orally in tablets or intravenously when oral administration was not possible due to the clinical condition of the patient. DXM starting dose consisted of 3 or 4 mg twice daily with or without an initial

(higher) bolus intravenously. Whether a bolus was applied and the duration of DXM therapy depended on the opinion of the treating physician and the clinical condition of the patient. Additional surgery by BHC took place when there was insufficient response to DXM treatment (i.e., persistence or deterioration of symptoms), but also based on the discretion of the treating physician to obtain optimal clinical outcome.

Study outcomes

The primary outcome of the study was clinical outcome ex- pressed by a dichotomized modified Rankin Scale (mRS) score (mRS 0–3 vs. 4–6) and MGS score at three months [21]. Secondary outcomes, if applicable, were mRS and MGS scores at discharge, if applicable MGS score prior to surgery and six months follow-up, CSDH recurrence, and additional treatment, including a repeated DXM scheme, number of additional surgeries performed after initial DXM treatment (crossover to surgery), and re-operation after a previous (first) surgery. An additional intervention was performed if there was an insufficient response of the initial treatment strategy, defined as persistence or progression of clinical symptoms. Further, we evaluated mortality, complications, and duration of hospital stay. CSDH recurrence was defined as recurrence of symptoms and neurological signs after initial improvement with recurrence or increase of CSDH on follow up CT. All data were processed in a clinical trial management system (Castor EDC, Amsterdam, The Netherlands).

Data collection

We collected all patient data from electronic medical records. Baseline patient characteristics included age, sex, history of trauma, use of anti-coagulant and/or anti-platelet therapy, clinical condition prior to symptom onset (living situation/ housing, mobility, mRS), and radiologic CSDH parameters (CSDH laterality, thickness, midline-shift, acute components). A dichotomized mRS and MGS score were formed by evaluation of patient records by the treating physician, rehabilitation specialist, nurses, and physical and ergo therapist at discharge, if applicable, prior to surgery and at three and six months, with a deviation of 6–16 and 20–30 weeks, respectively. The study protocol was reviewed by the local Medical Ethics Committee (METC Zuid West Holland, No. 17-022), and informed consent was waived.

Statistical analysis

The following assumptions were made for sample size calculation: An estimated good functional outcome (mRS 0–3) achieved in 80% of the primary surgery study group and 55% after initial DXM therapy was considered as an equal good outcome. With a two- sided alpha of 0.05 and beta error of 20% (power of 80%), a calculated sample size of 54 patients in each group was necessary to test the null hypothesis of equal probability of a good functional outcome. We enrolled consecutive series of the first 60 patients in HMC to cohort A and 60 patients in ETZ to cohort B in line with the centers local policy as first-line treatment. For the baseline characteristics quantitative data was analyzed with Mann-Whitney U tests and categorical data with Fisher's exact test or chi-squared tests. We performed regression analysis for the primary and secondary outcome parameters, adjusting for age, sex, and baseline symptom severity expressed by MGS score. SPSS 25.0 (IBM Corporation, NY) was used for statistical analysis.

Results

Patients were screened from January 2014 to December 2016 until the 60th, consecutive inclusion was reached in both centers. Of the 308 patients who had a CSDH, 188 did not meet the inclusion criteria because of the severity of symptoms (MGS 0, 3 or 4), presence of a subdural hygroma or concurrent presence of other intracranial lesions such as traumatic intra-parenchymal, or subarachnoid hemorrhage. Sixty consecutive patients in each hospital were included in cohort A or B.

Baseline characteristics were similar in both groups (table 1). In cohort A 60 patients received primary surgery (without DXM as an adjunct to surgery) and 60 patients in cohort B initiated DXM therapy. In both cohorts, anti-coagulant or anti-platelet therapy was ceased immediately after CSDH diagnosis. Resumption of anti-coagulant or antiplatelet therapy took place in all patients in cohort A, compared with 76% in cohort B (p=0.004). The time-interval until resumption also was significantly shorter in cohort A, with 7 days (range 7–34) compared to 22 days (3–100 range) in cohort B ($p < 0.001$). The median follow-up periods for the three- and six months evaluations were 66 (interquartile range [IQR] 54–85) and 194 days (IQR 166–253), respectively.

Table 1. Baseline characteristics

	Cohort A: Surgery (n=60)	Cohort B: DXM (n=60)
Age, y (mean, range)	73 (34-95)	72 (34-92)
Sex, F (%)	11 (18%)	15 (22%)
Evident history of head trauma, n (%)	45 (75%)	47 (78%)
Duration trauma until presentation, d (median, min-max)	1 (0-51)	6 (0-79)
Anti-coagulant or anti-platelet therapy, n (%)	31 (52%)	25 (42%)
Ceased at diagnosis, n (%)	31/31 (100%)	25/25 (100%)
Resumption of therapy, n (%)	31/31 (100%)	19/25 (76%)*
Duration until resumption, d (median; min-max)	7 (3-34)	22 (3-100)**
Comorbidities		
Cardiac history	34 (57%)	32 (53%)
Stroke (ischemic, hemorrhagic)	17 (28%)	13 (22%)
Diabetes mellitus	13 (22%)	9 (15%)
Neurodegenerative	6 (10%)	5 (8%)
Malignancies	11 (18%)	13 (22%)
Clinical condition prior to CSDH:		
mRS 0-3, n (%)	48/58 (83%)	48/60 (80%)
mRS 4-6, n (%)	10/58 (17%)	12/60 (20%)
Living situation:		
Independent, n (%)	56/60 (93%)	54/60 (90%)
Nursing home, n (%)	4/60 (7%)	6/60 (10%)
Mobilization:		
Independent	59/60 (98%)	57/60 (95%)
With aid of person or wheel chair, n (%)	1/60 (2%)	3/60 (5%)
Clinical condition at admission:		
MGS: 1, n (%)	17/60 (28%)	17/60 (28%)
MGS 2, n (%)	43/60 (72%)	43/60 (72 %)
mRS: 0-3, n (%)	17/60 (28%)	22/60 (37%)
mRS 4-6, n (%)	43/60 (72%)	38/60 (63%)
Radiological findings		
CSDH Right, n (%)	25 (42%)	26 (43%)
CSDH Left, n (%)	14 (23%)	17 (28%)
Bilateral CSDH, n (%)	21 (35%)	17 (28%)
Thickness, mm (median, min-max)	24 (8 – 38)	25 (10 – 40)
Midline shift, n (%)	55 (92%)	57 (95%)
Midline shift, mm (median, min-max)	9 (0 – 19)	8 (0 – 17)
Acute on chronic, n (%)	18 (30%)	20 (33%)

* Significant difference with $p < 0.05$; ** Significant difference with $p < 0.001$.

Primary outcome

Results on primary outcome are described in table 2, figure 1, and figure 2. In cohort A, a favorable mRS score (0–3) was reported in 70% of patients at 3 months compared with 76% in cohort B.
A good MGS score (0–1) was observed in 96% at 3 months in both cohorts. From logistic regression analysis for a good outcome of mRS 0–3, age appeared to be an (independent) significant predictor (OR 0.95, 95% CI 0.90–0.99, p = 0.03) as was male sex for a worse MGS score (OR 0.27, 95% CI 0.10–0.74, p = 0.01). Difference in treatment strategy between the cohorts did not significantly predispose for a good functional outcome at 3 months for the mRS (OR 0.77, 95% CI 0.30–1.98, p=0.59), nor MGS score (OR 0.98, 95% CI 0.45–2.15, p=0.95).

Secondary outcomes

Results on secondary outcomes are described in figures 1 and 2 and tables 3 and 4. Logistic regression analyses showed age (OR 0.93, 95% CI 0.89–0.97, p = 0.001) and baseline MGS score (OR 2.66, 95% CI 1.0–7.05, p = 0.05) to be (independent) predictors for mRS score 0–3 at discharge, as were male sex (OR 0.37, 95% CI 0.14–0.98, p = 0.05) and age (OR 1.04, 95% CI 1.01–1.07, p = 0.01) for a rise in MGS score at discharge. No significant differences were found in clinical outcome at discharge (mRS OR 0.89, 95% CI 0.40– 1.98, p=0.77; MGS OR 0.82, 95% CI 0.40–1.72, p=0.60) and follow-up 6 months (mRS OR 1.42, 95% CI 0.34–5.91, p=0.63; MGS OR 1.24, 95% CI 0.29–5.37, p = 0.77) between both groups.

For the remaining secondary outcome, logistic regression revealed only age to be a (independent) predictor for mortality (OR 1.10, 95% CI 1.02–1.19, p = 0.2). At six months, CSDH recurrence occurred in 22% (13/60) in cohort A compared with 12% (7/60) in cohort B (OR 2.11, 95% CI 0.77–5.79, p=0.15), leading to a

Table 2. Primary outcome

Clinical condition	Cohort A: Surgery (n=60)	Cohort B: DXM (n=60)
At follow – up 3 months		
mRS: 0-3, n (%)	37/53 (70%)	38/50 (76%)
mRS: 4-6, n (%)	16/53 (30%)	12/50 (24%)
MGS 0, n (%)	29/53 (54%)*	29/54 (54%)
MGS 1, n (%)	22/53 (42%)	23/54 (42%)
MGS 2, n (%)	2/53 (4%)	2/54 (4%)
MGS 3-4, n (%)	0	0

*Because of rounding, percentages may not add to 100%.

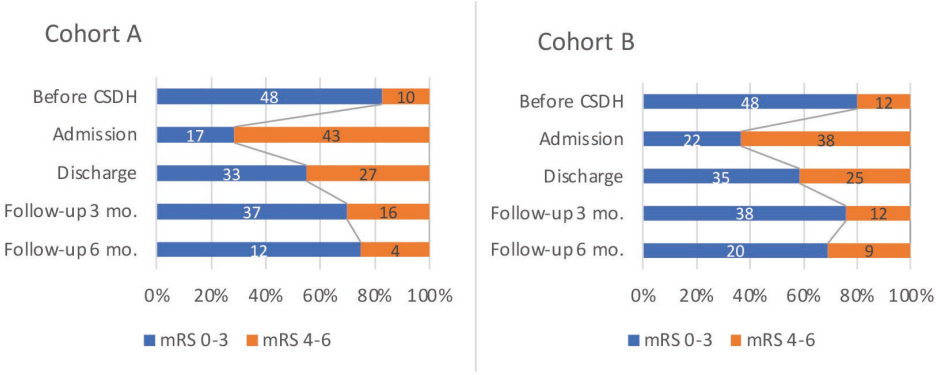

Figure 1. Modified Rankin Scale (mRS) score after primary surgery and initial DXM therapy. A. Cohort A (primary surgery); B. Cohort B (initial DXM). Green = mRS 0–3; Orange = mRS 4–6. Value in bars represents the absolute number of available patients with the relevant mRS score. Percentages indicate the proportion of patients with the relevant mRS value.

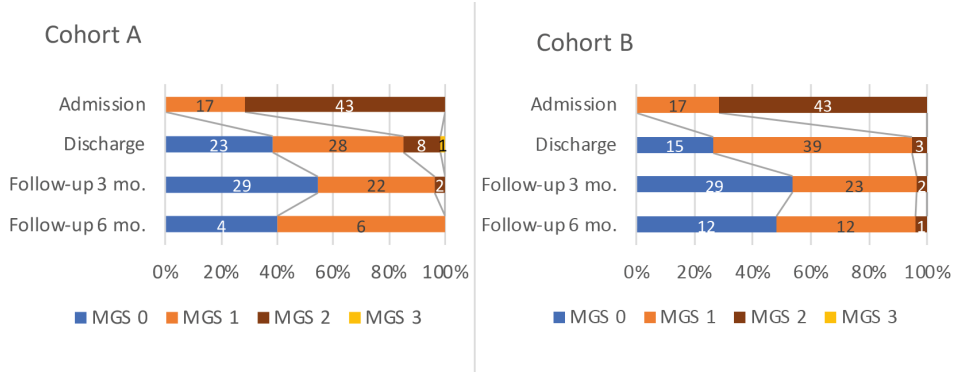

Figure 2. Markwalder Grading Score (MGS) cohort A (primary surgery) and B (initial DXM). Green = MGS 0; Light green = MGS 1; Red = MGS 2; yellow = MGS 3 (there were no patients with MGS 4). Value in bars represents the absolute number of available patients with the relevant MGS – score. Percentages indicate the proportion of patients with the relevant MGS value.

surgical re-intervention (re-operation) in nine of 13 patients in cohort A, and (additional surgery) in seven of seven patients in cohort B. Four patients with CSDH recurrence in cohort A received observation only due to the preference of the patient or treating physician. Total re-operation rate in cohort A was 11 because of one post-operative empyema and one acute hemorrhage in the BHC-trajectory necessitating a re-intervention. Of the 60 patients receiving primary BHC in cohort A, 88% (53/60) had an unchanged MGS score prior to surgery compared to baseline, 10% (6/60) had a 1-point worsening in MGS score (two

from MGS 1 to 2, four from MGS 2 to 3) and 2% (1/60) had a 1-point improvement (from MGS 1 to 0). This latter patient only reported headache at admission, which was absent prior to surgery on the next day. In cohort B ultimately 83% of patients (50/60) required a crossover to surgery after a median time period of six (IQR: 3–10) days of DXM therapy. Of these 50 patients, 80% (40/50) had an unchanged MGS score prior to surgery compared to baseline, 10% (5/50) had a 1-point worsening in MGS score (three from MGS 2 to 3, two from MGS 1 to 2 and 10% (5/50) had a 1-point improvement in MGS score (all from MGS 2 to 1). Two patients refused surgery and 48 underwent an additional operation.

Three patients had a re-operation (second surgery) in cohort B due to insufficient clinical improvement and hematoma persistence on follow-up CT. Surgery was prevented in 17% (10/60). Of these 10 patients, eight had an improvement in MGS score at discharge (five from MGS 2 to 1, two from MGS 1 to 0, one from MGS 2 to 0) and two had an unchanged MGS score compared to baseline (MGS 1). Overall, fewer patients in cohort A suffered from one or more complications

Table 3. Secondary outcomes.

	Cohort A: surgery (n=60)	**Cohort B: DXM (n=60)**	**OR (95% CI)**	**p**
Mortality, n (%)	6/60 (10%)	6/60 (10%)	1.04 (0.29-3.76)	0.96
CSDH recurrence, n (%)	13/60 (22%)	7/60 (12%)	2.11 (0.77-5.79)	0.15
Additional treatment, n (%) Repeated DXM scheme, n (%) Additional surgery after DXM, n (%) Re-operation after first surgery, n (%)	 n.a. n.a. 11/60 (18%)	 4/60 (7%) 50/60 (83%) 3/48 (6%)	 n.a. n.a. 3.55 (0.92-13.74)	 n.a. n.a. 0.06
Interval diagnosis-surgery, d (median, IQR)	1 (1-4)	6 (3-10)	OR 0.001 (<0.00-0.05)	<0.01
Duration DXM scheme, d (median, min-max)	n.a.	12 (1-155)	n.a.	n.a.
Length of hospitalization, d (median, min-max)	5 (2-35)	10 (1-47)	0.04 (0.00-0.66)	0.02
Number of patients with ³1 follow – up CT, n (%)	29/60 (48%)	51/60 (85%)	6.16 (2.53-14.95)	<0.01

(35% vs. 55%; OR 0.42, 95% CI 0.20–0.89, p=0.02). Hyperglycemia occurred in two patients with pre-existing diabetes mellitus (DM) in cohort A, versus 11 patients in cohort B of whom nine had known DM (3% vs. 18%, p=0.02). More urinary tract infections (1 vs. 7) were observed in the DXM group although the latter being not statistically significant. Mortality at 6 months was 10% in both groups (OR 1.04, 95% CI 0.29–3.76, p=0.96). More days of hospitalization were observed in the initial DXM group with a median of ten days per patient (range 1–47) versus five days (range 2–35) in the primary surgery group (OR 0.04, 95% CI 0.00–0.66, p=0.02). Radiologic monitoring by means of one or more follow-up CT-scan took place in significantly more patients (85%; 51/60) after initial DXM therapy compared with 48% (29/ 60) primary surgical (OR 6.16, 95% CI 2.53–14.95, p < 0.001).

Discussion

The present study demonstrates no difference in clinical outcome in symptomatic CSDH patients after initial DXM therapy compared with primary surgery. Although additional surgery was required in the vast majority of patients, an operation could be prevented in 17% receiving initial DXM therapy. Starting with a conservative approach however, seems to prolong the duration of hospitalization, leads to more intensive radiologic monitoring, and is associated with a higher complication rate in the present cohorts. CSDH

Table 4. Complications

	Cohort A: Surgery (n=60)	Cohort B: DXM (n=60)	p
Complications, n (number of patients)	21 (35%)	33 (55%)	0.02
Wound infection, n	0	2	0.50
Hemorrhage surgical area, n	0	2	0.50
Subdural empyema, n	3	0	0.24
Thromboembolic events	2	2	1.000
Epileptic seizure, n	7	5	0.76
Delirium	7	12	0.32
Urinary tract infection, n	1	7	0.06
Remaining infections, n	8	4	0.36
Cardiac complications, n	3	1	0.62
Fall, n	4	6	0.74
Hallucinations, behavioral changes, n	0	4	0.12
Hypoglycemia, n	1	0	1.000
Hyperglycemia, n	2	11	0.02
Remaining complications, n	0	1	1.000

recurrence occurred slightly more often in the primary surgical group (22% vs. 12%), although this was not statistically significant.

Consistent with previous research, our study revealed similar functional outcome in both treatment groups [12,13]. To our knowledge five observational studies have been performed to evaluate the effect of DXM therapy versus surgery in CSDH [12,13,18,22,23]. Only one retrospective and one prospective study evaluated the effect on functional outcome [12,13]. A good outcome, expressed by MGS 0-2 or Glasgow Outcome Scale (GOS) score 4-5, has been reported in 84-96% after initial DXM treatment compared to 77-93% after primary surgery [12-13]. Based on these results, authors recommended the use of DXM therapy as a conservative alternative treatment in selected patients. However, patients who received DXM in these studies were less severely affected (mainly MGS 1-2) compared to the surgical group (MGS 3-4), refused an operation or had a contraindication for surgery. These factors introduce a high load of selection bias and patient heterogeneity, and preclude a fair comparison between these treatments. The strength of our study is the highly comparable baseline profile making a comparison between groups fair.

We observed a very high cross-over rate in the initial DXM arm, with the prevention of surgery in 17% of patients. Higher success rates were revealed in two previous studies that showed 42 – 68% of patients to achieve complete recovery or MGS score 0-1 after DXM monotherapy [13-14]. Apart from the selection bias in given treatment strategy and unknown baseline symptom severity (MGS score) in one study, this discrepancy might also be explained by the higher dosing and possible longer duration of DXM therapy. In both previous studies DXM was administered in a daily dose of 12 mg/day during the first three days (in one study combined with prednisolone 30 mg/day), after which the dose was tapered down and treatment was stopped after two to four weeks. In our study DXM was dosed 6-8 mg/day with a median duration of 12 days. Taking into account the postulated pathophysiology in CSDH with inflammatory mediators, a more intensive corticosteroid treatment regimen could be more effective in reducing the subdural collection.

The high cross-over rate to surgery might also be due to a lower threshold to surgery maintained by treating physicians, without further awaiting the effect of DXM in the more severe cases. This led to additional surgery based on expert-opinion of the consulted neurosurgeon, who considered additional surgery to be the best treatment strategy to achieve good recovery taking into account the

current clinical condition as well as patient comorbidities and radiologic CSDH appearance. These observations underline the current lack of clear treatment strategies which causes inter-physician variation in treatment, and emphasize the need for an unambiguous treatment strategy for this vulnerable patient population.

Despite similarities in good clinical outcome, treatment burden seems to be higher in the initial DXM group. We found a significant longer duration of hospitalization when an initial conservative approach with DXM was applied (ten days) compared to primary surgery (five days). This finding is in contrast with previous studies that showed similar lengths of hospital stay, which ranged from 3.5-7 days after initial DXM treatment compared to 4-8 days after primary surgery [12-13]. This discrepancy could be attributed to the abovementioned heterogeneity in patient population reported in previous studies and the higher rate of surgery in this study after an initial DXM therapy. In accordance with the hospital treatment policy in cohort B, medically stable patients on DXM therapy were discharged home or to a rehabilitation facility if possible, awaiting the effect of DXM. However, regional differences in waiting time until a vacancy in these centers might have prolonged hospitalization in some patients. Finally, the higher occurrence of complications observed in patients with initial DXM therapy (35% versus 55%) compared to primary surgery, also influenced the duration of hospital stay. Data is scarce regarding DXM related complications in this patient group and varying results have been published previously [12,13,17,19]. Consistent with others hyperglycemia, which mainly was observed in patients with pre-existing DM, and (urinary tract) infections occurred most often after DXM treatment. The relatively high complication rate found in both groups in our study might also be due to our well-defined definitions of a complication, and the extensive and complete electronic documentation of patient records. Furthermore, the general anesthesia applied in cohort B might also influence the higher complication rate in this group [24]. All together, these findings highlight the fragility of this elderly population, also being illustrated by a mortality rate of 10%.

Interestingly, CSDH recurrence seemed lower after initial DXM therapy (12% versus 22%) as well as the operative recurrence rate (6% versus 18%), both not reaching statistical significance. Beneficial effect of DXM pre-operatively on CSDH recurrence risk has been postulated in previous retrospective studies without confirmation in randomized trials [13,16-19]. In our study however,

the earlier and higher resumption of anti-platelet and -coagulant therapy in the surgical group might impact the higher recurrence rate.

Based on our results higher health care costs are to be expected when treatment is initiated with DXM therapy and prospective, randomized data is desirable to obtain reliable insight into the health care costs. For this aim, the prospective randomized DECSA – trial has been initiated in 2016 to evaluate the effect of initial DXM therapy versus surgery on functional outcome as well as cost-effectiveness [25]. In this nationwide RCT symptomatic CSDH patients (MGS 1-3) will be randomized for corticosteroid therapy during 19 days (16 mg daily during four days, after which dose is tapered by half) or surgery by BHC with subdural drainage.

A limitation of this study is the retrospective design, which necessitated a dichotomized mRS score, allowing smaller differences in clinical outcome to be missed. Also, the absence of a fixed DXM dosing regimen and the inter-physician variation in the decision for a cross-over to surgery might have influenced the cross-over to surgery.

Conclusion

In this retrospective study we found no difference in good functional outcome after initial DXM therapy compared with primary surgery for symptomatic CSDH. Although surgery was pre- vented in 17% after initial DXM treatment, this strategy is still associated with a high rate of crossover to surgery, a significantly longer overall hospital stay and more complications. These results warrant a prospective, randomized controlled trial to firmly establish the optimal treatment strategy.

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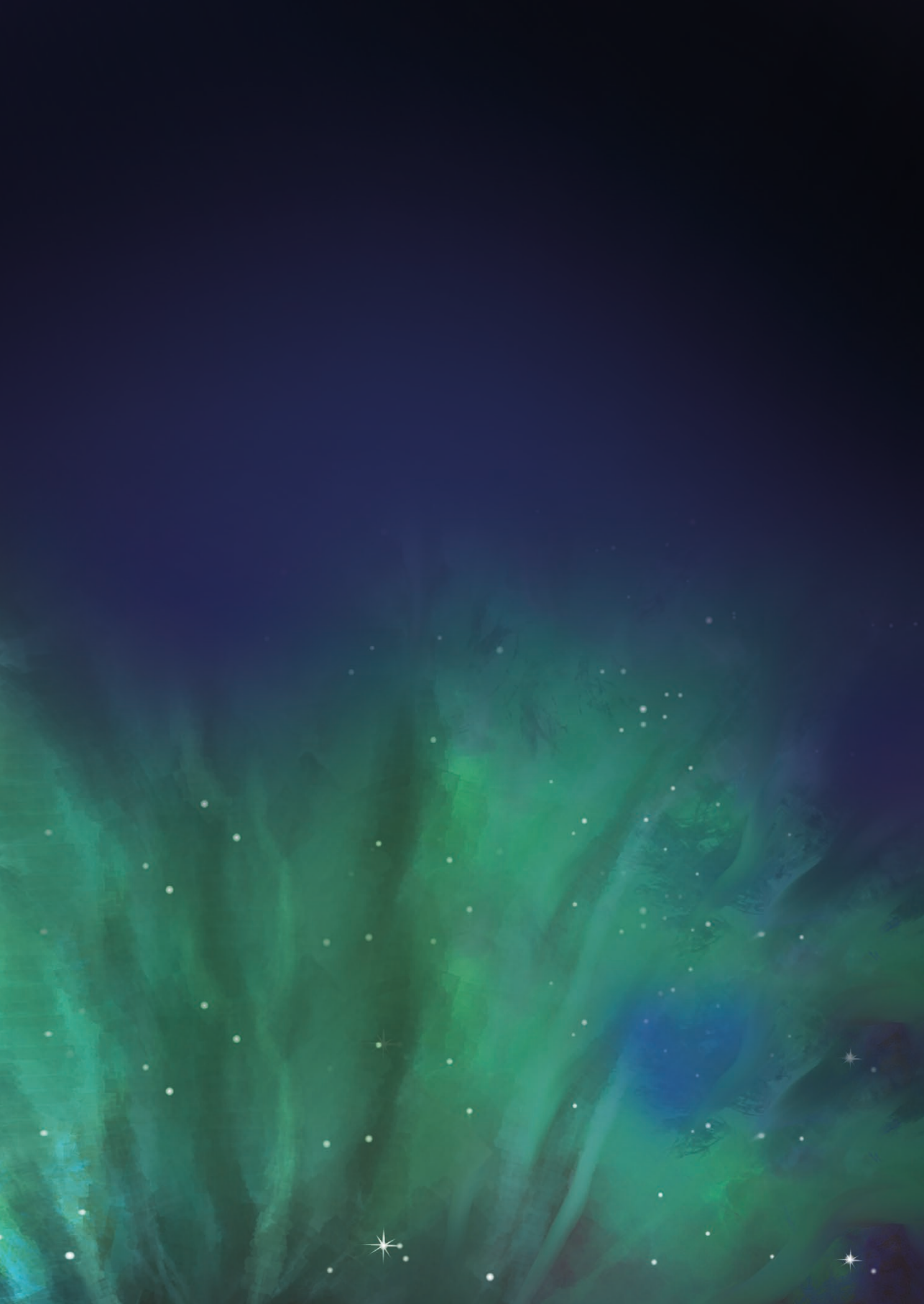

3

Dexamethasone therapy versus surgery for chronic subdural hematoma (DECSA trial): study protocol for a randomized controlled trial

Miah IP, Holl DC, Peul WC, Walchenbach R, Kruyt ND, de Laat K, Koot RW, Volovici V, Dirven CMF, van Kooten F, Kho KH, den Hertog HM, van der Naalt J, Jacobs B, Lingsma HF, Dammers R, Jellema K, van der Gaag NA.

Trials, 2018;19:575

Abstract

Background

Chronic subdural hematoma (CSDH) is a common neurological disease with a rapidly rising incidence due to increasing age and widespread use of anticoagulants. Surgical intervention by burr-hole craniotomy (BHC) is the current standard practice for symptomatic patients, but associated with complications, a recurrence rate of up to 30% and increased mortality. Dexamethasone (DXM) therapy is, therefore, used as a non-surgical alternative but considered to achieve a lower success rate. Furthermore, the benefit of DXM therapy appears much more deliberate than the immediate relief from BHC. Lack of evidence and clinical equipoise among caregivers prompts the need for a head-to-head randomized controlled trial. The objective of this study is to compare the effect of primary DXM therapy versus primary BHC on functional outcome and cost-effectiveness in symptomatic patients with CSDH.

Methods/Design

This study is a prospective, multicenter, randomized controlled trial (RCT). Consecutive patients with a CSDH with a Markwalder Grading Scale (MGS) grade 1 to 3 will be randomized to treatment with DXM or BHC. The DXM treatment scheme will be 16 mg DXM per day (8 mg twice daily, days 1 to 4) which is then halved every 3 days until a dosage of 0.5 mg a day on day 19 and stopped on day 20. If the treatment response is insufficient (i.e. persistent or progressive symptomatology due to insufficient hematoma resolution), additional surgery can be performed. The primary outcomes are the functional outcome by means of the modified Rankin Scale (mRS) score at 3 months and cost-effectiveness at 12 months. Secondary outcomes are quality of life at 3 and 12 months using the Short Form Health Survey (SF-36) and Quality of Life after Brain Injury Overall Scale (QOLIBRI), hematoma thickness after 2 weeks on follow–up computed tomography (CT), hematoma recurrence during the first 12 months, complications and drug-related adverse events, failure of therapy within 12 months after randomization and requiring intervention, mortality during the first 3 and 12 months, duration of hospital stay and overall healthcare and productivity costs. To test non- inferiority of DXM therapy compared to BHC, 210 patients in each treatment arm are required (assumed adjusted common odds ratio DXM compared to BHC 1.15, limit for inferiority < 0.9). The aim is to include a total of 420 patients in 3 years with an enrolment rate of 60%.

Discussion

The present study should demonstrate whether treatment with DXM is as effective as BHC on functional outcome, at lower costs.

Trial registration

EUCTR 2015-001563-39. Date of registration: 29 March 2015.

Keywords

Dexamethasone, DXM, Chronic subdural hematoma, CSDH, Burr-hole craniostomy, BHC

Background

A chronic subdural hematoma (CSDH) is a common neurological disease with a rapidly rising prevalence due to increasing age and the widespread use of anticoagulants [1–4]. It generally affects the elderly population and patients with coagulopathy, who often have co-existing medical diseases [1, 5]. The estimated incidence in Western countries is 8.1 per 100,000 per year in patients aged 65 years or older [6], but increases to 58/100,000/year for those aged 70 years or older [1, 7].

Surgical intervention by burr-hole craniotomy (BHC) followed by subdural drainage is the mainstay treatment in symptomatic patients with a CSDH [8, 9], which leads to a favorable functional outcome in 84% of patients [10]. However, despite the optimization of techniques surgery is still associated with relevant complications, recurrence rates up to 30%, and considerable mortality [8–12]. In addition, especially advanced age and the presence of comorbidities could render patient's ineligible for BHC.

Dexamethasone (DXM) therapy has been proposed as an alternative, non-operative or adjuvant treatment modality and might have the potential to block the anti-inflammatory changes in the formation of the hematoma and can specifically impede the formation of neo-membranes and neo-capillaries by its powerful inhibition of inflammatory mediators [13, 14]. Therefore, DXM is administered routinely in various institutions.

To date, only three retrospective and one prospective study have compared the clinical effect of DXM to BHC in CSDH patients [15]. No randomized trials have been published that compare both treatments. Therefore, we designed the DECSA trial: a randomized controlled, multicenter trial to evaluate the non-inferiority of primary DXM compared to primary BHC on functional outcome and cost-effectiveness in patients with symptomatic CSDH.

Methods/Design

Trial design

This is a prospective, multicenter, open-label, randomized controlled trial (RCT) with a blinded endpoint (PROBE design) assessment [16]. Eligible patients are

randomized to DXM therapy (the intervention arm) or BHC (control arm; see additional file 1 for SPIRIT check-list).

Primary study objective

The primary objective is to evaluate the non-inferiority of primary DXM therapy versus primary BHC on functional outcome as expressed by modified Rankin Scale (mRS) score (table 1) at three months and cost-effectiveness at 12 months in patients with symptomatic CSDH.

Secondary objectives

The secondary objectives of the study are functional and clinical outcome, expressed by mRS and Markwalder Grading Scale (MGS) scores (table 2), respectively, at discharge, at two weeks, three, six and 12 months and Glasgow Outcome Scale-Extended (GOSE) score (table 3) at three months. Furthermore, assessment of quality of life using the Short Form – 36 Health Survey (SF-36) and Quality of Life after Brain Injury Overall Scale (QOLIBRI) will take place at three and 12 months and healthcare and productivity costs at three and 12 months. Hematoma thickness will be evaluated after two weeks on follow-up computed tomography (CT). Mortality will be evaluated during the first three and 12 months. During the total follow-up period of 12 months, we will also evaluate hematoma recurrence, complications and drug-related adverse events, failure of therapy after randomization and requiring intervention, duration of hospital stay and overall healthcare and productivity costs.

Table 1. Modified Rankin Scale (mRS)

Score	Functional status
0	No symptoms.
1	No significant disability. Able to carry out all usual activities, despite some symptoms.
2	Slight disability. Able to look after own affairs without assistance, but unable to carry out all previous activities.
3	Moderate disability. Requires some help, but able to walk unassisted.
4	Moderately severe disability. Unable to attend to own bodily needs without assistance, and unable to walk unassisted.
5	Severe disability. Requires constant nursing care and attention, bedridden, incontinent.
6	Death.

Table 2. Markwalder Grading Scale

Score	Clinical status
0	Patient neurological normal.
1	Patient alert and oriented; mild symptoms such as headache; absent of mild neurological deficit such as reflex asymmetry.
2	Patient drowsy (defined as Glasgow Coma Scale, GCS, score: 13-14) or disoriented with variable neurological deficit, such as hemiparesis.
3	Patient stuporous (defined as GCS 9 – 12) but responding appropriately to noxious stimuli; severe focal signs such as hemiplegia.
4	Patient comatose (GCS 8 or lower) with absent motor responses to painful stimuli; decerebrate or decorticate posturing.

Table 3. Glasgow Outcome Scale – Extended

Score	Category	Score	Category
1	Death	5	Moderate disability, lower
2	Vegetative state	6	Moderate disability, upper
3	Severe disability, lower	7	Good recovery, lower
4	Severe disability, upper	8	Good recovery, upper

Study setting and participants

Patients will be recruited for the study from the emergency department, neurological or neurosurgical outpatient clinic or ward or through referral from general hospitals of the seven participating Dutch neurosurgical hospitals. The seven participating neurosurgical hospitals are Haaglanden Medical Center (HMC) The Hague, Haga Teaching Hospital The Hague, Leiden University Medical Center (LUMC) in Leiden, Medisch Spectrum Twente (MST) Enschede, Erasmus Medical Center (EMC) Rotterdam, Isala Hospital Zwolle and University Medical Center Groningen (UMCG). The study is open to additional participating neurosurgical centers.

Inclusion criteria

Eligible patients must be 18 years or older and meet all of the following criteria:

1. The presence of a newly diagnosed CSDH, defined as an iso-dense or hypodense hematoma in the subdural space on cranial computed tomography (CT) scan. Hyperdense components may be present but must compromise less than one third of the hematoma

2. Clinical symptoms must be explained by the CSDH
3. The patient is eligible for BHC and DXM based on clinical symptoms and radiological appearance of CSDH
4. MGS grade 1–3.

The MGS is a validated grading system (score 0–4, see table 2) for the severity of neurological symptoms and is used to classify the neurological condition for CSDH patients [17].

Exclusion criteria

Exclusion criteria are:

1. MGS grade 0 or 4
2. An acute subdural hematoma
3. The presence of a minimal CSDH on cranial CT which is technically not drainable by BHC
4. Pregnancy
5. Cerebrospinal fluid shunt in situ (e.g. ventriculoperitoneal shunt)
6. Known hypersensitivity to DXM
7. Known ulceration in the gastro-intestinal tract
8. Poorly regulated diabetes mellitus (DM) defined as a glycosylated hemoglobin (HbA1C) value > 8% (64 mmol/mol)
9. Clinical suspicion of an acute systemic infection (fever, leukocytosis, elevated C-reactive protein)
10. History of gastro-intestinal bleeding
11. Glaucoma
12. Previous history of severe affective disorders (i.e. psychosis).

Participant timeline

The time schedule in figure 1 describes all study processes, assessments and interventions. The flow diagram (figure 2) displays the main study procedures, including follow-up evaluations. In summary, study patients will be evaluated at presentation (baseline), during their hospital stay, at discharge and during the follow-up period at two weeks, three months, six months and 12 months.

At two weeks (after initiation of the study treatment) patients will be evaluated by neurological examination combined with a follow-up CT scan at the outpatient clinic or ward and at three months at the outpatient clinic. A mRS-certified research nurse, blinded for treatment allocation, will evaluate the primary outcome (mRS score) at three months by phone. At three and 12

months, patients will receive questionnaires on quality of life. Additionally, an evaluation of mRS score will take place by phone at three, six and 12 months. Healthcare and productivity costs will be evaluated at three and 12 months. We expect to complete patient inclusion in three years. The estimated duration of the study (including follow-up) will be four years.

Interventions

Investigational treatment

Patients in the intervention arm will receive DXM in a daily dosage of 16 mg (8 mg every 12h) on days one to four. Thereafter, DXM will be tapered by half every three days (see table 4 for the DXM dosing scheme) until a dosage of 0.5 mg a day on day 19 and stopped on day 20. DXM is administered orally in tablets or intravenously when oral administration is not possible. If the patient improves on DXM therapy (defined by ≥ 1 point decrease in MGS score) during the first two weeks, the treatment will be continued until day 19. During DXM treatment a proton pump inhibitor (pantoprazole, 40 mg daily) is administered as prophylaxis.

DXM therapy can be discontinued for the following reasons: (1) no improvement of the clinical condition, defined as an unchanged MGS score 2 weeks after initiation of DXM therapy with unchanged or increased hematoma on the follow-up CT at two weeks, (2) clinical deterioration, defined by as ≥ 1 point increase in MGS score, at any time after initiation of DXM treatment, (3) the occurrence of severe, relevant DXM-related side effects or complications (i.e. uncontrollable hyperglycemia, gastro-intestinal bleeding or psychiatric symptoms), (4) pre-study complement discontinuation of DXM therapy is primarily left to the discretion of the treating physician and is recommended in case of: persistence of moderate to severe neurological symptoms (MGS grade 2–3) in combination with the presence of relevant severe, current comorbidities (i.e. an infection, metabolic deterioration) which could interfere with the expected recovery, and a surgical intervention could be beneficial and the safest option for patient recovery.

In any case of pre-study discontinuation of DXM therapy, the reason for this is documented. Whenever DXM is discontinued, a cross-over to the reference treatment (BHC) can occur depending on the remaining symptoms, which is the local standard of care in the participating hospitals.

Study procedure	Initial screening	During admission	Day of surgery	Day 1-2 post-surgery	At discharge	FU (2 weeks)	FU (3 months)	FU (6 months)	FU (12 months)
Medical history	X								
Demographics	X								
Concomitant medications	X	X	X		X				
Neurological examination	X	X (OD[1])	X		X	X[2]	X[3]		
Vital parameters	X	X (OD[4])	X		X				
CT - scan	X					X[5]			
Laboratory evaluation	X	X[6]	X[7]	X[7]					
Glucose monitoring	X	X[8]							
Informed consent	X[9]								
MGS	X		X		X	X	X	X[11]	X[11]
mRS	X				X	X	X[10]	X[11]	X[11]
GOSE							X[10]		
Quality of life (SF-36, QOLIBRI)	X[12]						X[12]	X[12]	X[12]
Costs	X[10]						X[12]		X[12]
Complications		X			X	X	X	X	X
Adverse events		X			X	X	X	X	X
Serious adverse events		X			X	X	X	X	X
Mortality		X			X	X	X	X	X

Figure 1. Time schedule of study procedures. FU = Follow up. OD = Once a day.

[1] In case of clinical deterioration, neurological examination can be repeated more often a day.

[2] Evaluation will take place during admission or at the outpatient clinic.

[3] Evaluation will take place at the outpatient clinic.

[4] If medically necessary, vital parameters can be examined several times a day.

[5] In case of clinical deterioration, a follow up CT scan can be performed before or after the planned follow-up CT at two weeks.

[6] If medically necessary additional blood samples will be taken during admission (i.e. INR check, glucose, infection parameters).

[7] Only in case of oral anticoagulation use, an INR will be checked on day of surgery and day one and two post-operative.

[8] In case of known diabetes mellitus (DM) or DXM therapy (and DM) daily glucose monitoring will take place.

[9] If the patient cannot provide written informed consent due to neurological symptoms related to the CSDH, the legal representative can give initial informed consent. As soon as the patient recovers from the symptoms, informed consent will be obtained from the participant during follow – up at two weeks or 3 months.

[10] Evaluation will take place by phone by a trained research nurse, blinded for treatment allocation.

[11] Evaluation will take place by phone.

[12] Evaluation will take place by using questionnaires regarding quality of life or healthcare and productivity costs.

Reference treatment

Patients randomized to the reference treatment arm are operated on preferably within the first seven days, depending on anticoagulant or antithrombotic therapy use, severity of symptoms and discretion of the treating physician. Surgery will take place through BHC followed by insertion of a subdural drain for two days in line with the standard protocols in each participating hospital. Antibiotic prophylaxis is administered preoperatively. Either general or local anesthesia will be applied. One or two 14-mm burr holes, depending on the surgeon's discretion, are drilled over the maximum width of the hematoma. The dura mater is opened with a cruciate incision and coagulated with bipolar diathermy. The subdural collection is washed out with warm Ringer's lactate saline, with or without a catheter. The subdural outer and inner membrane loculations, if present, can be disrupted when easily accessible via the burr holes. Whenever the saline has dispersed sufficiently a subdural drain is placed and the wound is closed.

Reoperation can be indicated when neurological deficits do not resolve, deteriorate or recur within the follow-up duration. Treatment options consist of redo burr-hole evacuation, if necessary, through another additional hole, percutaneous aspiration, craniotomy, or craniectomy.

Concomitant care

All included patients will otherwise receive routine standard of care. Patients with mild neurological deficits (MGS grade 1) on admission can be discharged home in anticipation of the planned BHC or awaiting the effect of DXM therapy. However, in MGS grade 1 patients with known diabetes mellitus (DM) with HbA1C<64 mmol/ mol randomized for DXM therapy, monitoring for blood glucose levels is necessary during the first three days after treatment initiation. Glucose monitoring can take place clinically during admission or if possible, at the nursing home. Patients with MGS grade 2–3 (in either arm) remain in

Table 4. Dexamethasone dosing scheme. DXM: dexamethasone.

Day	DXM dosage	Day	DXM dosage
1 – 4	8 mg every 12 hours	14 – 16	0.5 mg every 12 hours
5 – 7	4 mg every 12 hours	17 – 19	0.5 mg per day
8 – 10	2 mg every 12 hours	20	stop
11 – 13	1 mg every 12 hours		

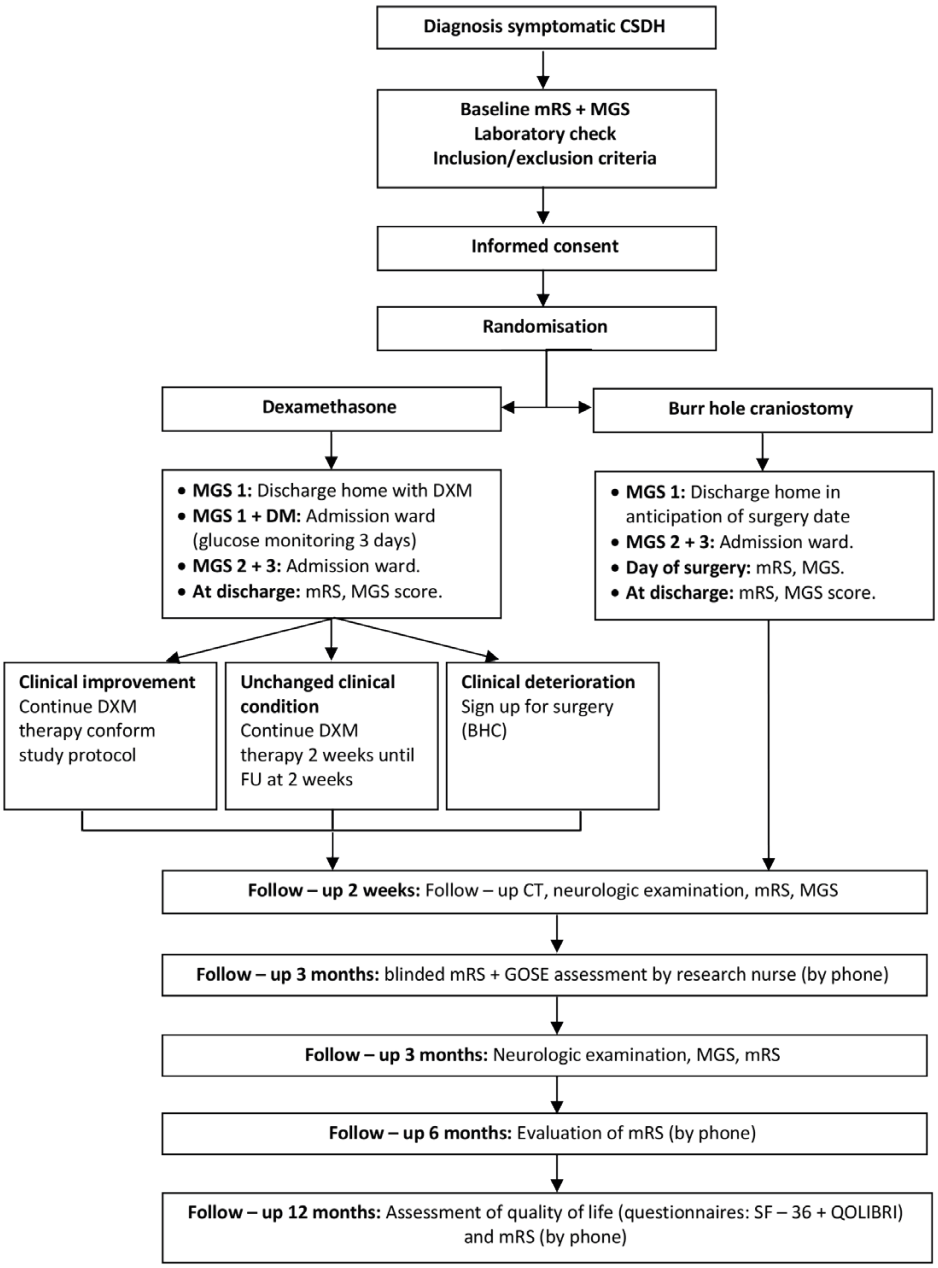

Figure 2. Flow diagram of main study procedures.

hospital until the treating physician judges the clinical situation safe for discharge.

During admission neurological investigations and vital parameters are recorded daily. Low-molecular-weight heparin (LMWH) will be applied in both patient groups as thrombosis prophylaxis if the patient is not optimally mobile. Patients will receive physiotherapy, speech therapy or rehabilitation consultation if deemed necessary.

Antithrombotic therapy

Oral antithrombotic therapy will be discontinued in both study arms from the moment of randomization to prevent hematoma growth and to avoid interference with planned surgery. In case of vitamin K antagonist (VKA) therapy the international normalized ratio (INR) is corrected to ≤1.5 through the administration of vitamin K and/or prothrombin complex concentrate (PCC), as is the current practice. For patients using platelet-aggregation-inhibitor therapy, surgery is preferably planned seven days after discontinuation of therapy, if allowed by the clinical condition. At the discretion of the surgeon, earlier intervention is allowed if deemed clinically necessary. The reason for early surgery has to be recorded in the case report form (CRF). Non-vitamin-K oral anticoagulants (NOAC) are discontinued at least one day prior to surgery.
Any antithrombotic therapy can be resumed two weeks after the initiation of DXM therapy or surgery following a follow-up CT without signs of CSDH recurrence, recent onset hematoma or unchanged mass effect with midline shift compared to the initial CT at randomization. Partial resolution of CSDH at this stage without recent hematoma is not a contraindication for resumption. For absolute indications (e.g., mechanic cardiac valve) earlier resumption or bridging of therapy within these 14 days is allowed. Any reason for early resumption has to be recorded in the CRF. Subgroup analyses will be performed to evaluate the effect of anti-thrombotic therapy in both groups.

Outcomes

Primary outcome measures

The primary endpoints are the functional outcome, expressed by mRS, at three months after start of study treatment and cost-effectiveness at 12 months.

Secondary outcome measures

Secondary outcomes include: functional and clinical outcome, expressed by mRS and MGS scores, respectively, at discharge, at two weeks, at three, six

and 12 months after start of study treatment. We will also determine a utility-weighted mRS (UW-mRS) at three months. The GOSE score will be assessed at three months, quality of life (expressed by SF-36 and QOLIBRI) at three and 12 months, cost-effectiveness at three and 12 months and hematoma thickness at two weeks. During the first 12 months, we will evaluate hematoma recurrence (defined as recurrence of symptoms and neurological signs after initial improvement with persistence, recurrence or increase of CSDH on follow-up CT), failure of therapy after randomization and requiring intervention, complications and drug-related adverse events, duration of hospital stay and healthcare and productivity costs in both patient groups. Finally, we will evaluate mortality during the first three and 12 months.

Randomization

Patients are randomized in a 1:1 allocation ratio stratified for study site by their treating physician. Stratified block-randomization is done by using a computer randomization algorithm to generate balanced random samples (Castor EDC, Ciwit B.V., Amsterdam, The Netherlands).

Sample size

This RCT is designed as a non-inferiority study. The sample size for showing non-inferiority is calculated based on a simulation program in R statistical software for power for ordinal regression. We aim to include 420 patients. This sample size yields a power of 90%, assuming that the true effect of DXM is an odds ratio 1.15 for a better functional outcome on the mRS, and the limit for inferiority is an odds ratio < 0.9.

Data collection

All patient data is collected in the electronic data capture software Castor EDC (Ciwit B.V., Amsterdam, The Netherlands). This software allows built-in logical checks and validations to promote data quality. Data entry is performed locally by trained research nurses and physicians. No patient-identifying information is collected.

Data analysis

The primary effect parameter (and all other comparisons of the treatment arms) will be performed on all randomized subjects according to the intention-to-treat (ITT) principle. A sensitivity analysis is performed for the primary outcome

measure in a per-protocol fashion, defined as patients in the ITT population receiving treatment as randomized without protocol violation.

The primary effect parameter will be the adjusted common odds ratio (acOR) for a shift in the direction of a better outcome on the mRS at three months with 95% confidence interval, estimated with multivariable ordinal logistic regression with adjustment for important prognostic baseline variables. This analysis is becoming the standard for ordinal functional outcomes in neurology and neurosurgery, supported by evidence for its maximization of statistical power while maintaining interpretability. Missing data in baseline characteristics will be imputed using multiple imputation (n = 10) based on the outcome and relevant baseline covariates using the 'Multivariate Imputation by Chained Equations' (MICE) algorithm. Patients with missing primary outcome will be excluded but every effort will be made to obtain follow-up. To accept the null hypothesis (H0) of non-inferiority the lower 95% confidence limit of the odds ratio for a better functional outcome on the mRS of DXM versus surgery should be equal to or above 0.9.

Furthermore, we will perform an extensive economic evaluation of DXM versus surgery for patients with a CSDH. The economic evaluation will be performed according to the Dutch guidelines, using a societal perspective. The timeframe will be 12 months to take all relevant costs and effects into account. The primary effect measure for the economic evaluation will be functional status (mRS). Secondary outcome measures for the cost-effectiveness analyses (CEA) will be mortality and quality-adjusted life year (QALY), based on the 12-month SF-36 and QOLIBRI summary scores. The cost-effectiveness will be assessed by calculating the incremental cost-effectiveness ratio (ICER), defined as the difference in costs, divided by the average change in effectiveness of DXM versus surgery in CSDH patients. The cost-effectiveness analysis will use the mRS as effect measure and the cost-utility analysis will use the QALY as effect measure.

Uncertainty around this ratio will be presented using confidence eclipses on the cost-effectiveness plane and acceptability curves. We will perform a sensitivity analysis to assess the robustness of the results to changes in costs and effectiveness parameters. Due to the short time horizon, no discounting for costs and effects will be used (see additional file 2 for statistical analysis plan).

For secondary endpoint parameters, Kaplan-Meier and Cox regression analysis will be used for mortality comparisons between the treatment arms, binary logistic regression for complications and failure of therapy, and a linear regression to evaluate quality of life. A p value of less than 0.05 will be used to indicate statistical significance. For all analyses, R statistical software will be used.

Study monitoring

Data monitoring

The coordinating investigator will visit study centers every three months to discuss any issues and check on conduct of the study. Prior to recruitment, the field team (physicians) will receive information and instructions on the objectives of the study, methods and processes of the study. CRF data will be monitored by an independent external expert at regular intervals throughout the study to verify adherence to the protocol and data complete- ness, consistency and accuracy.

Data Safety Monitoring Board (DSMB)

In order to increase the safety of the intervention the trial will be monitored by an independent Data Safety Monitoring Board (DSMB). The DSMB will work in accordance with a dedicated charter and will follow processes recommended by the DAMOCLES Statement. The DSMB will be chaired by a neurosurgeon, and include a neurologist and an independent methodologist/ statistician. The DSMB will meet at least annually or after inclusion of the next 150 patients (whichever comes first). With respect to study safety and efficacy, interim analyses of major endpoints (including serious adverse events believed to be due to treatment) are performed after 150 and 300 patients have completed their follow-up evaluation. In addition, the DSMB will review the study logistics/ trial conduct in terms of: assessment of compliance with the study protocol (including adherence to inclusion and exclusion criteria) and monitor data quality (completeness), time to start of the procedure (DXM/surgery), cross-overs, occurrence and listing/registration of (serious) adverse events, by center and by treatment arm.

Adverse events (AEs) and serious adverse events (SAEs)

Adverse events are defined as any undesirable event occurring to a patient during the study, whether or not considered related to DXM therapy or surgery. All adverse events reported spontaneously by the patient or observed by the investigator or staff will be recorded. A SAE is any untoward medical

occurrence or effect that results in death; is life-threatening (at the time of the event); requires hospitalization or prolongation of existing in patients' hospitalization; results in persistent or significant disability or incapacity or any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention, but could have been based upon appropriate judgement by the investigator. SAEs are reported by the investigators in participating centers to the coordinating investigator. SAEs will be reported through the web portal ToetsingOnline to the accredited Medical Ethics Committee that approved the protocol.

Interim analysis

Interim analyses of major endpoints (including serious adverse events believed to be due to treatment) are performed after 150 and 300 patients have completed their follow-up evaluation.

Dissemination of results

Trial results will be published in an international journal, communicated to neurological and neurosurgical associations and presented at (inter)national congresses.

Discussion

General guidelines defining the preferred treatment for CSDH are lacking, but worldwide, surgery is the current standard practice. Various hospitals, however, apply DXM as an alternative treatment modality or as an adjunctive therapy prior to surgery. To date, no head-to-head trial comparing the two modalities in a well-defined cohort of patients has been performed to our knowledge. The competing benefit of either treatment is, therefore, not clear.

CSDH development occurs likely due to (mild) traumatic brain injury causing a tear in the dural border cell layer which leads to extravasation of cerebrospinal fluid and blood in the subdural space. At a point neurological deficits arise because of a mass effect due to liquefaction and progressive enlargement of an initially small hematoma. The rationale behind corticosteroid therapy is based on results of previous experimental work that postulates an inflammatory response to be responsible for the hematoma enlargement [13, 14, 18–23]. Accumulated blood in the subdural space, in particular erythrocyte breakdown products, incites an inflammatory reaction that results in the deposition of fibrin

and formation of subdural neo-membranes with in-growth of neo-capillaries. These neo-membranes are vulnerable structures with high vascularization of the outer layer and are prone to rupture and bleed. Furthermore, it is also believed that the outer layer of the neo-membrane contains a high content of plasminogen and plasminogen activator, which cause an enzymatic fibrinolysis and liquefaction of the initial blood clot in the inner hematoma. This situation finally results in frequent effusions of plasma or rebleeding from the neo-membranes into the subdural collection. Hence, a cascade of inflammation, impaired coagulation, angiogenesis and fibrinolysis plays an important role in the formation of CSDH.

Despite this dynamic hypothesis regarding the pathophysiology of CSDH, high-quality data supporting the use of DXM therapy as alternative treatment to surgery is scarce. Previous studies have shown favorable results of DXM as adjunctive to surgery in reducing mortality [24] and reoperation rate [15, 25, 26]. In current literature only four (non-randomized) studies evaluated the effect of corticosteroids in CSDH management as monotherapy compared to corticosteroids as an adjunctive to surgery or surgery alone [15]. In each study a different primary outcome measure was applied, of which only two used a validated outcome scale to assess functional outcome.

Of these two studies, the first study had a prospective design and evaluated 112 patients in four patient groups: DXM monotherapy, DXM in combination with surgery by BHC without additional drainage, surgery only and observation only [27]. This study revealed a favorable outcome, defined by a Glasgow Outcome Scale (GOS) score of 4–5 at six months, in 88% after DXM monotherapy. The reported success rate (GOS 4–5) for DXM therapy adjunctive to surgery was 91%, compared to 77% after surgery alone and 50% after observation only. The second study described a retrospective evaluation in 122 patients in slightly different patient groups: initial DXM therapy, surgery alone by twist-drill mini-craniostomy, surgery alone by craniotomy and observation only [28]. A favorable outcome was expressed by a Markwalder Grading Scale (MGS) score of 0–2 at discharge and was achieved in 73% after DXM monotherapy. In 25% of patients receiving initial DXM therapy, monotherapy failed and additional surgery was required in this group. In the primary surgical groups the reported success rates (MGS score 0–2) were 93 and 75% after twist-drill mini-craniostomy and craniotomy, respectively, and for the observation only group 100%.

In contrast, extensive research has been performed regarding the several operative techniques. Different surgical techniques can be applied, such as craniotomy, BHC or twist-drill craniostomy, with or without placement of a subdural drain. To date, no class I evidence exists to compare the various methods of hematoma evacuation. A recent large systematic review evaluated all 24 available RCTs regarding surgical treatment of CSDH. The only significant finding was a reduction in hematoma recurrence after postoperative subdural drainage based on eight RCTs [9]. In addition, one of the largest RCTs, performed in 215 symptomatic CSDH patients, showed that subdural drainage compared to no drainage not only lowered recurrence rate, but also reduced mortality and improved functional outcome at six months [10].

Overall, surgical techniques have been thoroughly demonstrated as effective therapy in the current literature for CSDH patients. DXM is showing promising results as an alternative treatment, but confirmation of these results is essential by means of RCTs.

Trial status

This trial started on 1 September, 2016. The first patient was included in Medical Center Haaglanden (HMC) The Hague and subsequently enrolment was started in Haga Teaching Hospital The Hague and Leiden University Medical Center (LUMC) Leiden. The trial will start on 1 August 2018 at Erasmus Medical Center (EMC) and Medisch Spectrum Twente (MST) and on 1 September 2018 at Isala Hospital Zwolle and Groningen University Medical Center (UMCG). The study is open to additional participating neurosurgical centers.

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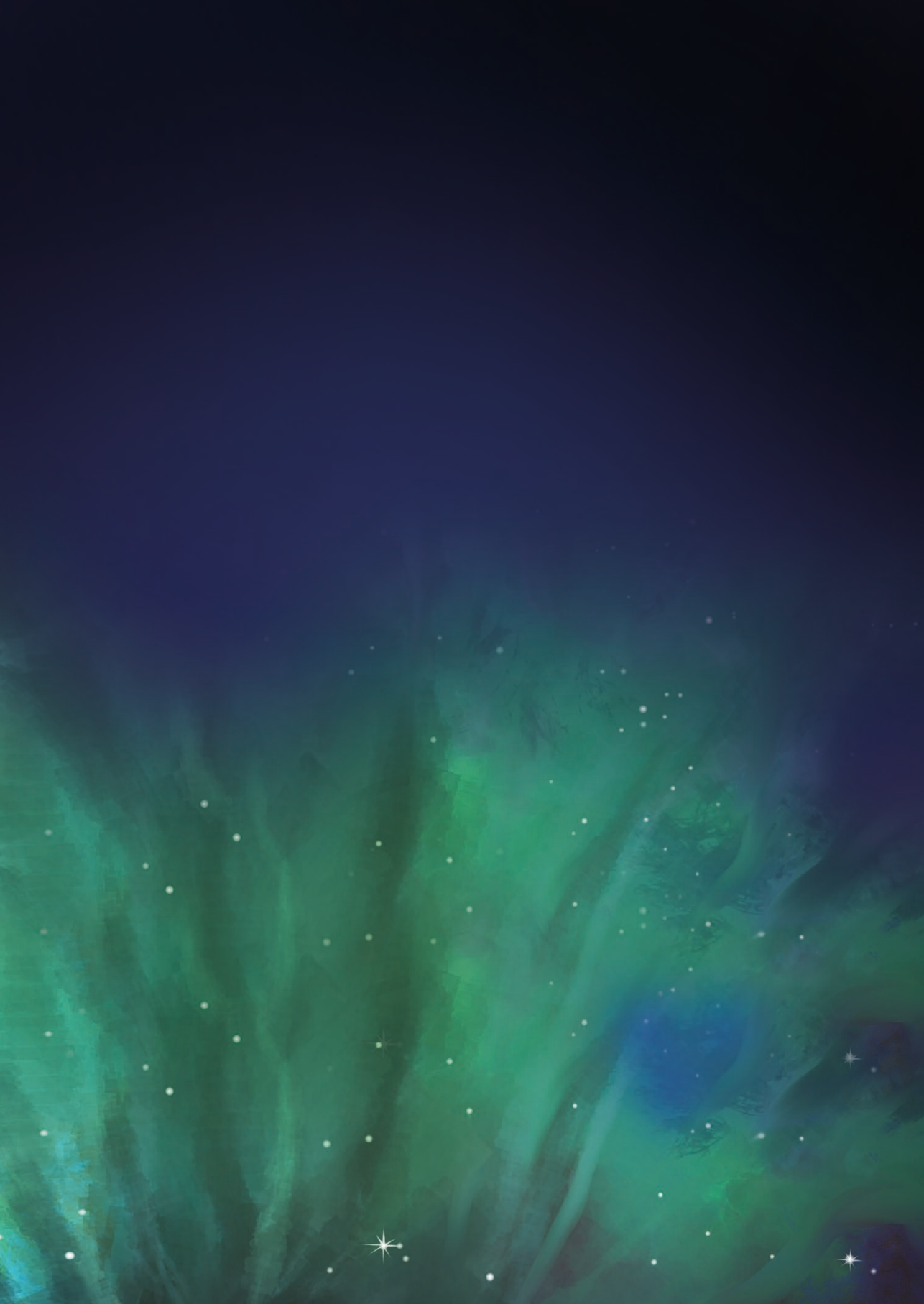

4

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

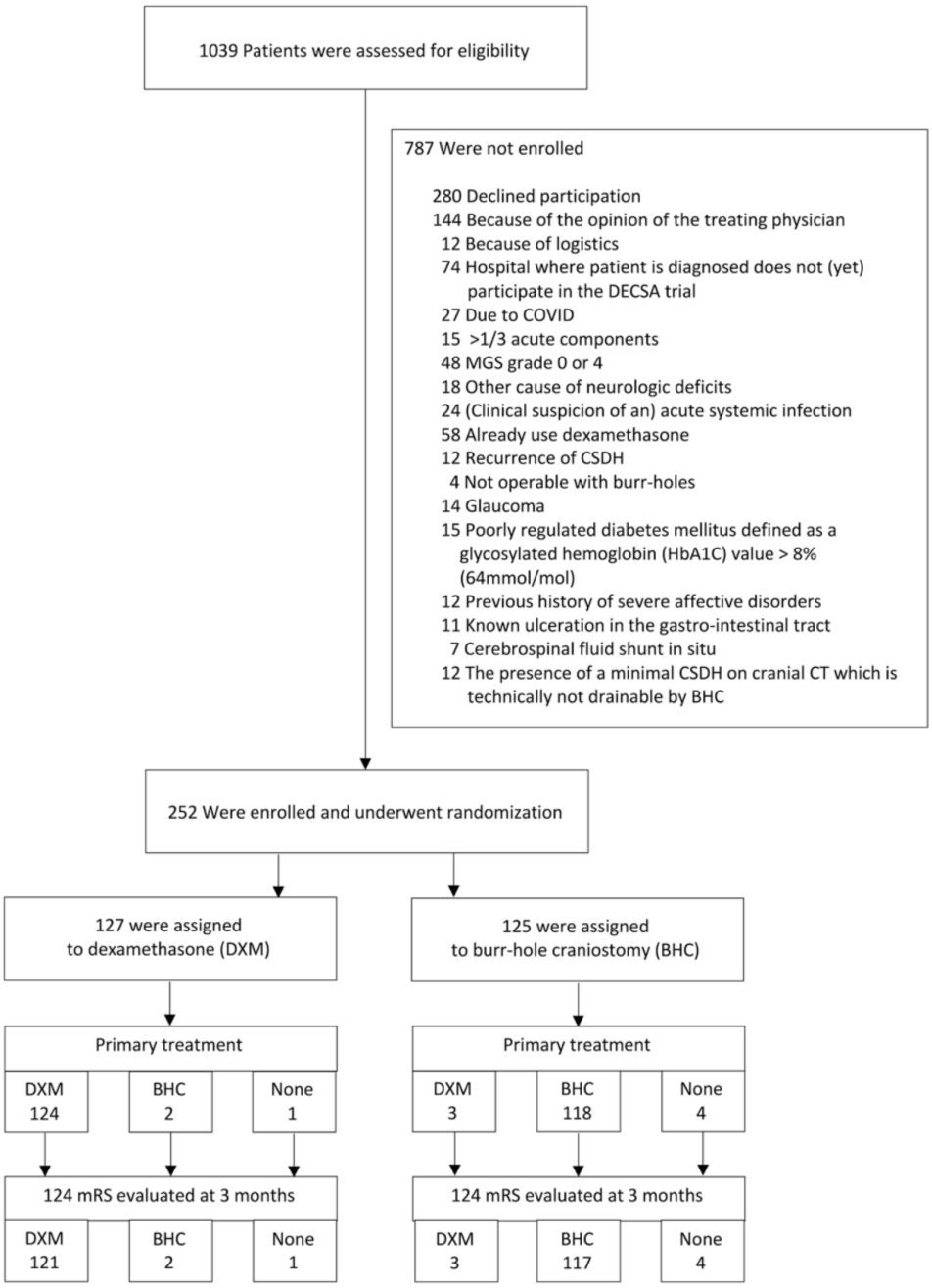

Figure 1. Flowchart of randomized patients, their primary treatment and follow-up status.

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).

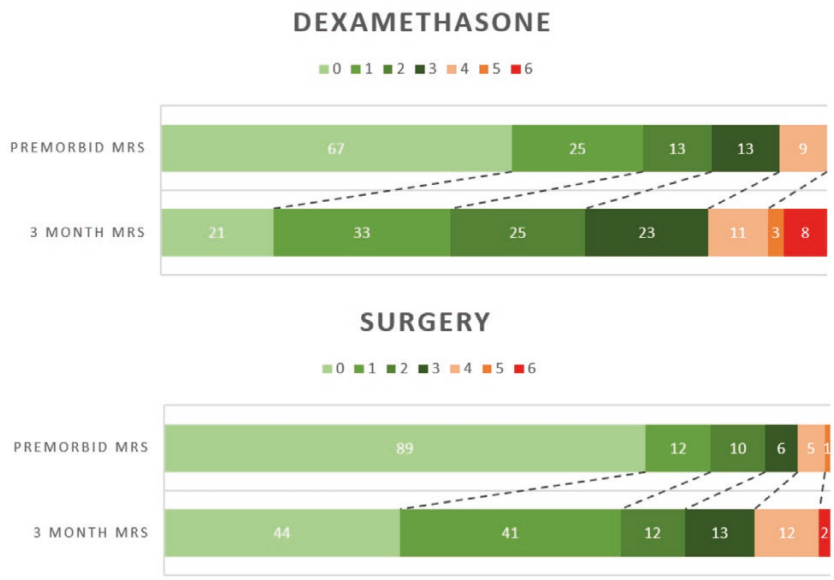

Figure 2. modified Rankin Scale. Comparison between dexamethasone and surgery in the premorbid phase and at 3 months

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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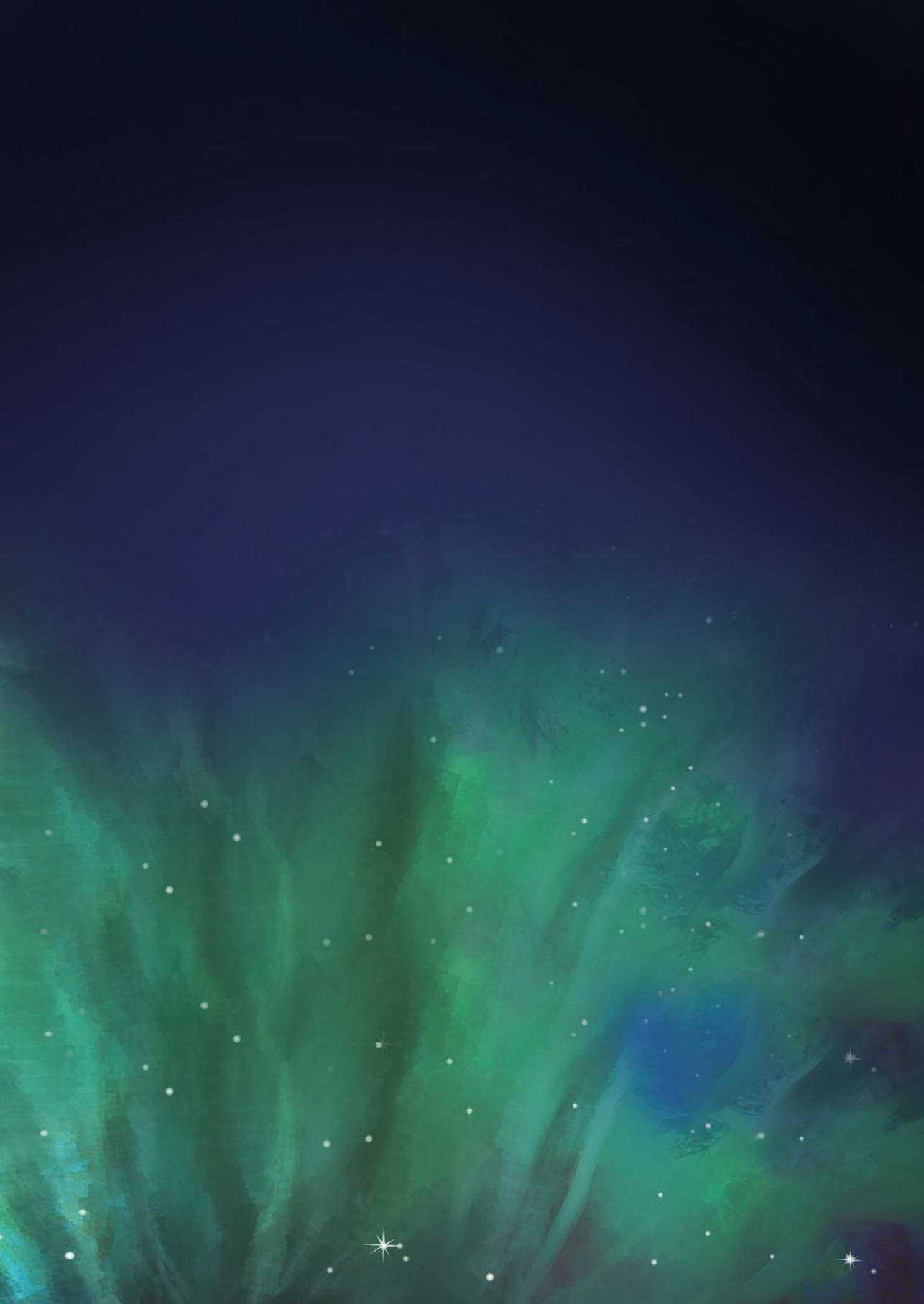

5

Radiological prognostic factors of chronic subdural hematoma recurrence: a systematic review and meta-analysis

Miah IP, Tank Y, Rosendaal FR, Peul WC, Dammers R, Lingsma HF, den Hertog HM, Jellema K, van der Gaag NA.

Neuroradiology, 2021;63:27-40.

Abstract

Purpose

Chronic subdural hematoma (CSDH) is associated with high recurrence rates. Radiographic prognostic factors may identify patients who are prone for recurrence and who might benefit further optimization of therapy. In this meta-analysis, we systematically evaluated pre-operative radiological prognostic factors of recurrence after surgery.

Methods

Electronic databases were searched until September 2020 for relevant publications. Studies reporting on CSDH recurrence in symptomatic CSDH patients with only surgical treatment were included. Random or fixed effects meta-analysis was used depending on statistical heterogeneity.

Results

Twenty-two studies were identified with a total of 5566 patients (mean age 69 years) with recurrence occurring in 801 patients (14.4%). Hyperdense components (hyperdense homogeneous and mixed density) were the strongest prognostic factor of recurrence (pooled RR 2.83, 95% CI 1.69–4.73). Laminar and separated architecture types also revealed higher recurrence rates (RR 1.37, 95% CI 1.04–1.80 and RR 1.76 95% CI 1.38–2.16, respectively). Hematoma thickness and midline shift above predefined cut-off values (10 mm and 20 mm) were associated with an increased recurrence rate (RR 1.79, 95% CI 1.45–2.21 and RR 1.38, 95% CI 1.11–1.73, respectively). Bilateral CSDH was also associated with an increased recurrence risk (RR 1.34, 95% CI 0.98–1.84).

Limitations

Limitations were no adjustments for confounders and variable data heterogeneity. Clinical factors could also be predictive of recurrence but are beyond the scope of this study.

Conclusions

Hyperdense hematoma components were the strongest prognostic factor of recurrence after surgery. Awareness of these findings allows for individual risk assessment and might prompt clinicians to tailor treatment measures.

Key points

• Recurrence of chronic subdural hematoma (CSDH) after surgery occurs frequently with reported rates that vary between 2.5 and 33%.

• Establishment of radiographic prognostic factors may identify more complex patients prone to CSDH recurrence.

• Many radiological parameters of CSDH have been reported to be associated with the recurrence risk, with conflicting results due to discrepancies in recurrence rate and study heterogeneity.

• In this meta-analysis of 22 studies, we found hyperdense and mixed density hematoma to be associated with the highest risk of CSDH recurrence after surgery, as were laminar and separated hematoma architecture types.

• Awareness of these findings allows for individual risk assessment and might prompt clinicians to tailor treatment measures.

Keywords Chronic subdural hematoma – CSDH – Recurrence – Predictors – CT

Introduction

Chronic subdural hematoma (CSDH) is a frequently encountered neurosurgical disorder of the elderly with a rising incidence [1, 2]. Historically, CSDH was considered as a progressive and recurrent hemorrhage due to rupture of cortical bridging veins initiated by trauma [3]. Recently however, it has been suggested that a more complex pathway of inflammation, angiogenesis, recurrent micro-hemorrhages, and local coagulopathy in the subdural space is involved [4–8]. This inflammatory response is presumed to play a key role in hematoma formation, re-bleeding, and maintenance.

The diagnosis is based on clinical symptoms and radiological investigation, mostly non-contrast CT scan. Surgery through burr hole drainage or twist drill craniostomy (BHC, TDC) is the mainstay of treatment worldwide [9, 10]. Alternative strategies include watchful observation or high-dose glucocorticoids administration depending on symptom severity and local protocols [11–14]. Ultimately, the aim of all therapeutic modalities is adequate symptom relieve by effective hematoma resolution.

Recurrence of CSDH after surgery occurs frequently with reported rates that vary between 2.5 and 33% [15–17]. Postoperative closed drainage as interventional measure is effective in reducing recurrence risk by roughly 50% [1, 10, 17]. Recurrent CSDH poses a formidable challenge in the treatment of symptomatic patients [18]. Recurring symptoms and additional treatment increase patient burden, prolong hospital admissions leading to higher costs, and contribute to a potential poor outcome [19, 20]. Therefore, the identification of factors associated with recurrence is important for individual risk assessment, treatment decisions, and possibly optimization of pre- and postoperative management. An individualized approach could entail adjusting the timing of surgery and anti-thrombotic therapy resumption or even exploring alternative treatment strategies depending on local protocols.

Many radiological parameters of CSDH have been reported to be associated with the recurrence risk, including uni- or bilateral hematoma, preoperative hematoma thickness and midline shift, hematoma density and internal architecture, cerebral atrophy, and hematoma volume [21–34]. However, studies have shown conflicting results and large discrepancies in recurrence rates due to heterogeneity in treatment, radiological measurement techniques, and variation in hematoma classifications for hematoma density or architecture.

In this systematic review and meta-analysis, we aimed to identify radiological prognostic factors of CSDH recurrence in surgically treated symptomatic CSDH patients.

Materials and methods

Before conducting this systematic review, we developed a detailed protocol including objectives and a strategy for collecting and analyzing data. The manuscript was prepared in accordance with the Preferred Reporting Items for Systematic Review and Meta-analysis Protocols (PRISMA) guidelines.

Search strategy and selection criteria

Literature on symptomatic CSDH patients and radiological findings published until September 2020 were reviewed using PubMed, EMBASE, Web of Science, and Cochrane library. Potential studies were searched using the following keywords and MeSH terms (including abbreviations, variations due to plurality and spelling): "chronic subdural hematoma," "imaging," "radiological," "predictor," "computed tomography," and "magnetic resonance imaging." The search was supplemented by hand searching the reference list of each included article and review article. Our primary outcome was CSDH recurrence. Inclusion criteria for study selection were the following: (1) symptomatic CSDH patients, (2) only surgical therapy by burr hole or twist- drill craniostomy with subdural drainage, (3) pre-defined (and retrievable) definition of CSDH recurrence, (4) follow-up period of ≥ 3 months, (5) clinical studies with > 10 subjects, and (6) evaluation of at least one of the following radiological parameters: uni- versus bilateral hematoma, hematoma thickness, mid- line shift, hematoma density and architecture on CT, hematoma volume, MRI appearance (T1, T2, diffusion-weighted imaging, DWI). Studies performed in animals, case reports or reported in other than English language were excluded.

Data extraction

Data from the included studies were extracted by one neurologist (IPM) and one radiologist (YT) using a standardized data extraction form. Disagreements were resolved by consensus. The following data were collected: (1) study characteristics (country, study design, year of publication, number of participants, definition of CSDH (diagnostic criteria) and CSDH recurrence, type of surgery, follow-up period, radiological parameters evaluated), (2) patient characteristics (mean age, sex, trauma, use of oral anticoagulation,

or platelet aggregation inhibitors), and (3) imaging findings of radiological parameters: uni- versus bilateral hematoma, hematoma thickness (frequencies below or above prespecified cutoff value in mm), midline shift (present/absent or frequencies below or above prespecified cut-off value in mm), hematoma density classification and hematoma architecture types, volume (in mm3, frequencies above or below prespecified cut off value), and MRI appearance (hypo-, iso- or hyperintensity on T1, T2, and DW- imaging). Hematoma density was categorized as (1) homogeneous hypodense, (2) homogeneous isodense, (3) homogeneous hyperdense, and (4) mixed density. Hematoma architecture was reported using the four classifications as described by Nakaguchi [26] (table 1, figure 1): (a) homogeneous architecture, (b) laminar architecture, (c) separated architecture, and (d) trabecular architecture. Due to heterogeneity and lack of standardization in reporting on hematoma density and architecture, we added two simplified categories to summarize density and architecture findings: (i) a (total) homogeneous group containing all patients with a homogeneous hypodense, homogeneous iso-dense, and homogeneous hyperdense hematoma; (ii) (total) mixed density group, containing all mixed density hematoma and the following architecture types with mixed density: laminar, separated, grading, and trabecular hematoma.

Quality of reporting in included studies

We assessed risk of bias and quality of reporting of all included studies based on the Newcastle–Ottawa Quality Assessment Scale (NOS) checklist, used to build a quality score between 0 and a maximum of 9 stars [35]. When there was risk of selection bias in patient inclusion (i.e., exclusion of patients with head trauma, anticoagulant or platelet aggregation inhibitor use, bilateral CSDH, or absence

Table 1. Hematoma classification by architecture type

Architecture types	Description
Homogeneous	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 was mingled at the border, this was called a gradation type
Trabecular	Hematoma with inhomogeneous components and a high-density septum running between the inner and outer hematoma membrane

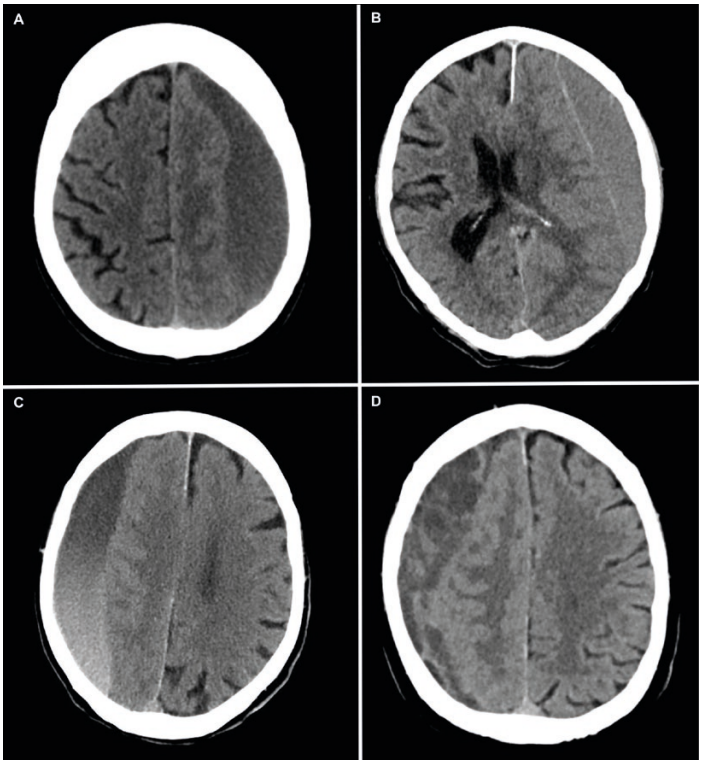

Figure 1. Hematoma architecture types. A. homogeneous; B. laminar; C. separated; D. trabecular.

of follow-up CT), one star was subtracted in the selection-section (max. 4 stars). Stars were assigned in the comparability section if adjustments took place for confounders (max. 2 stars). If there was no statement regarding the number of patients who were actually evaluated at the predefined follow up moment (3, 6, or 12 months), one star was also subtracted in the outcome-section (max. 3 stars). Studies were rated with good quality if they had 3 or 4 stars in the selection domain and 1 or 2 stars in the comparability domain and 2 or 3 stars in the outcome/exposure domain. Studies were of fair quality when they scored 2 stars in the selection domain and 1 or 2 stars in the comparability domain and 2 or 3 stars in the outcome/ exposure domain. Studies were also classified as fair quality when they had maximum stars in the selection and outcome domain, with no stars in the comparability section. Finally, studies were classified as poor quality when they scored 0 or 1 star in the selection domain or 0 stars in comparability domain or 0 or 1 star in outcome/exposure domain.

Statistical analysis

Analyses were performed using SPSS (version 25.0, IBM Corp) and Review Manager (RevMan, version 5.3. Copenhagen: The Nordic Cochrane Center, The Cochrane Collaboration, 2014). Continuous and categorical variables were summarized with means and counts and percentages respectively. To evaluate recurrence risk, we calculated risk ratios (RR) with 95% confidence intervals for the following comparisons: (1) unilateral versus bilateral hematoma, (2) hematoma thickness below versus above prespecified cutoff values (15, 20, and 25 mm), (3) presence versus absence of midline shift, (4) midline shift below versus above prespecified cut off values (5, 10, and 15 mm), (5) mixed density (total) versus homogenous density (total) hematoma, (6) homogeneous hyper- and mixed density versus homogeneous iso- and hypodensity hematoma, (7) architecture types (homogeneous versus non-homogeneous; laminar versus non-laminar; separated versus non-separated; trabecular versus non-trabecular), (7) hematoma volume below versus above prespecified cut off values (121 mm3 [28]), and (8) hematoma MRI-hypo- and -iso-intensity versus hyper- and mixed intensity on T1, T2, and DW-imaging. Statistical heterogeneity in each meta-analysis was assessed using the T2, I2, and chi-square tests. When heterogeneity was moderate to high (I2 50% or higher), a random effects model was used; if this was lower than 50%, a fixed effects model was applied.

Results

We identified 3112 publications published between 1 January 1940 and September 2020, of which 100 were evaluated in full text and 22 finally included in the meta-analysis (figure 2 flow-chart of included studies). All studies scored three to four stars on the selection category of the NOS questionnaire. Scores on the outcome category varied between two to three, depending on the reporting on follow-up. None of the studies adjusted for confounders, resulting in no stars for the comparability section. Study quality was classified as fair for three (14%) and poor for 19 (86%) studies (table 2).

Study and patient characteristics

All 22 studies were cohort studies, of which three (14%) had a prospective follow-up design (table 3). Four definitions were identified for CSDH recurrence after primary surgery: (1) surgery (reoperation), without additional clinical or radiological criteria (n = 6); (2) clinical symptoms and/or radiological signs requiring additional surgery (n = 1); (3) combination of clinical recurrence

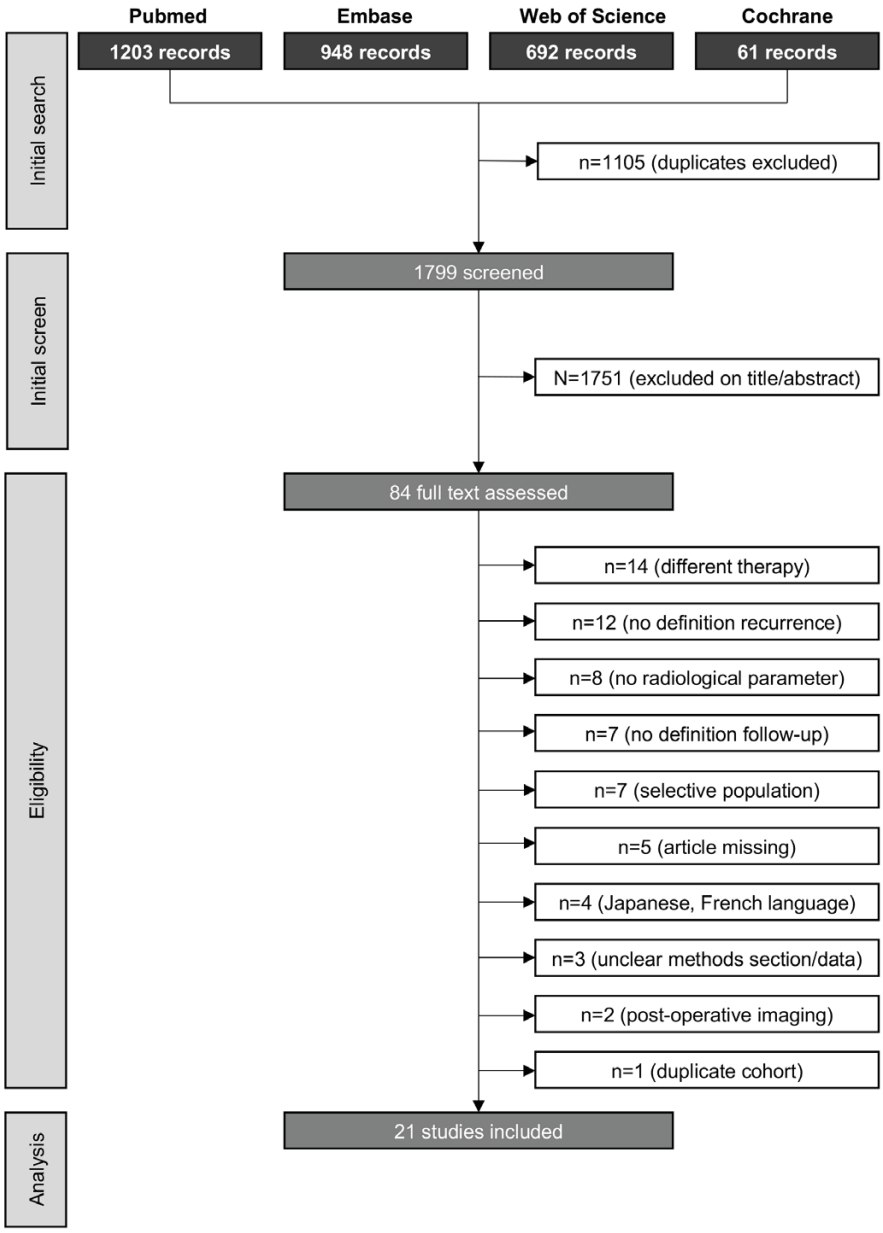

Figure 2. Newcastle–Ottawa Quality Assessment Scale (NOS), cohort studies

or progression of symptoms and radiological recurrence or progression of ipsilateral CSDH (n = 10); and finally (4) only radiologic recurrence or progression of CSDH (n = 5). In three of these latter five studies, all patients received additional surgery due recurrent or progressive symptoms [29,

Table 2. Newcastle – Ottawa Quality Assessment Scale (NOS), cohort studies

Study	Selection	Comparability	Outcome	Study quality
Shen et al., 2019 [15]	★★★★	-	★★★	Fair
You et al., 2018 [21]	★★★★	-	★★	Poor
Yan et al., 2018 [22]	★★★	-	★★★	Poor
Lee et al., 2018 [30]	★★★★	-	★★	Poor
Bartek et al., 2017 [66]	★★★★	-	★★	Poor
Hammer et al., 2017 [46]	★★★	-	★	Poor
Kim et al., 2017 [54]	★★★★	-	★★	Poor
Han et al., 2017 [13]	★★★★	-	★★★	Fair
Stavrinou et al., 2017 [67]	★★★★	-	★★	Poor
Goto et al., 2015 [29]	★★★★	-	★★	Poor
Jung et al., 2015 [19]	★★★	-	★★	Poor
Song et al., 2014 [23]	★★★	-	★★	Poor
Jeong et al., 2014 [26]	★★★	-	★★	Poor
Huang et al., 2014 [24]	★★★★	-	★★★	Fair
Stanisic et al., 2013 [68]	★★★★	-	★★	Poor
Chon et al., 2012 [17]	★★★★	-	★★	Poor
Ko et al., 2008 [18]	★★★★	-	★★	Poor
Amirjamshidi et al., 2007 [14]	★★★	-	★★	Poor
Yamamoto et al., 2003 [50]	★★★★	-	★★	Poor
Nakaguchi et al., 2001 [20]	★★★	-	★★	Poor
Oishi et al., 2001 [38]	★★★★	-	★★	Poor

45, 49]. One study reported a reoperation in 16 out of 21 cases (76%) due to reappearance of symptoms with observation only in the remaining patients [26]. The fifth study mentioned a reoperation was performed if reappearance of symptoms accompanied the radiological CSDH recurrence, without describing the number of patients requiring surgery however [20]. An overview of the radiological parameters evaluated in this meta-analysis is provided in table 3. Follow-up period ranged from 3 to 12 months. Six patients died prior to discharge [21, 45], leading to a total inclusion of 5566 CSDH patients in the meta-analysis with CSDH recurrence occurring in 801 (14.4%; table 4). Overall male-

Table 3. Study characteristics

Study	Country	Period	Design	Patients (n)	Definition CSDH	Definition reCSDH	Follow-up (mo)	Radiological parameter
Shen, 2019 [15]	China	2012-2018	Ret.	461[a]	No	R+C	3	L, T, M, D, A
You, 2018 [21]	China	2013-2016	Ret.	226	No	R+C+S	12	L, M, D, A
Yan, 2018 [22]	China	2010-2017	Ret.	231	No	R+C	3	L, T, M, D, A, V
Lee, 2018 [30]	Korea	2012-2015	Ret.	131	Yes[b]	R+C	6	D, MRI-DWI
Bartek, 2017 [66]	Sweden	2005-2010	Ret.	759	No	S	6	L, D
Hammer, 2017 [46]	Germany	2009-2012	Pro.	73	No	S	1.5	D, A
Kim, 2017 [54]	Korea	2010-2015	Ret.	248[c]	No	R	6	L, D
Han, 2017 [13]	Korea	2004-2014	Ret.	756	No	S	6	T, M
Stavrinou, 2017 [67]	Germany	2011-2014	Ret.	195	No	S	3	L, D, A
Goto, 2015 [29]	Japan	2004-2010	Ret.	414	No	R+C	6	L, MRI-T1+T2
Jung, 2015 [19]	Korea	2008-2012	Ret.	182	No	S	12	L, M, D, A
Song, 2014 [23]	Korea	2009-2012	Ret.	97	Yes[b]	R	3	L, T, M, D
Jeong, 2014 [26]	Korea	2008-2012	Ret.	125	No	R+C	3	L, M, D
Huang, 2014 [24]	Taiwan	2005-2006	Ret.	94	Yes[d]	R+C	3	L, M
Stanisic, 2013 [68]	Norway	2008	Pro.	107	Yes[b]	R+C	7	L, M, D, A
Chon, 2012 [17]	Korea	2006-2011	Ret.	420	No	R+C	3	L, T, M, D, A
Ko, 2008 [18]	Korea	2001-2006	Ret.	255	Yes[b]	R+C	3	L, M
Amirjamshidi, 2007 [14]	Iran	2000-2006	Pro.	82	No	R	3	T, M, D
Yamamoto, 2003 [50]	Japan	1991-2000	Ret.	105	No	R	3	L, M
Nakaguchi, 2001 [20]	Japan	1989-1998	Ret.	106	Yes[b]	R	3	D, A
Oishi, 2001 [38]	Japan	1995-1999	Ret.	116	No	R+C	3	L, D

A: architecture; BHC+D: burr hole craniostomy combined with post-operative subdural closed drainage system; C: clinical recurrence/progression of symptoms; D: density; L: laterality; M: midline shift; Pros: prospective; R: radiologic recurrence/progression of CSDH; Retro: retrospective; S: symptoms and/or radiological signs requiring surgery; T: thickness;

[a]: four patients died before discharge, therefor analyses were performed in 457 patients.
[b]: definition CSDH: Radiologic finding of subdural fluid collection with peri-operative confirmation of CSDH.
[c]: two patients died before discharge, therefor analyses were performed in 246 patients.
[d]: definition CSDH: Diagnosis is based on pre-defined radiologic criteria with peri-operative confirmation of CSDH.

Table 4. Patient characteristics

Study	Patients (n)	Gender (M:F)	Age (y, m)	Trauma (n, %)	OAC (n, %)	PAI (n, %)	OAC or PAI (n, %)	reCSDH (n, %)
Shen, 2019 [15]	461[a]	376:81	69	235 (51)	-	-	28 (6)	69 (15)
You, 2018 [21]	226	184:42	65	161 (71)	-	-	14 (6)	34 (15)
Yan, 2018 [22]	231	188:43	-	-	-	-	-	33 (14)
Lee, 2018 [30]	131	85:46	68	71 (54)	-	-	35 (27)	7 (5)
Bartek, 2017 [66]	759	514:245	74	-	116 (15)	194 (26)	310 (41)	85 (11)
Hammer, 2017 [46]	73	47:26	75	-	-	-	-	19 (26)
Kim, 2017 [54]	248[b]	173:73	69	187 (75)	6 (2)	53 (21)	59 (24)[c]	31 (13)
Han, 2017 [13]	756	574:182	68	-	81 (11)	220 (29)	301 (40)	104 (14)
Stavrinou, 2017 [67]	195	134:61	71	99 (51)	48 (25)	56 (29)	104 (53)	35 (18)
Goto, 2015 [29]	414	279:135	77	-	14 (3)	70 (17)	84 (20)	37 (9)
Jung, 2015 [19]	182	131:51	68	125 (69)	10 (5)	36 (20)	46 (25)	25 (14)
Song, 2014 [23]	97	64:33	70	61 (63)	-	-	-	16 (16)
Jeong, 2014 [26]	125	92:33	69	81 (65)	-	35 (28)	35 (28)	8 (6)
Huang, 2014 [24]	94	79:15	69	70 (74)	2 (2)	12 (13)	14 (15)	13 (14)
Stanisic, 2013 [68]	107	72:35	72	86 (80)	15 (14)	36 (34)	51 (48)	17 (16)
Chon, 2012 [17]	420	334:86	67	237 (56)	34 (8)	117 (28)	151 (36)	92 (22)
Ko, 2008 [18]	255	150:105	65	181 (71)	8 (3)	-	8 (3)	24 (9)
Amirjamshidi, 2007 [14]	82	67:15	59	52 (63)	-	-	-	10 (12)
Yamamoto, 2003 [50]	105	73:32	71	78 (74)	-	-	4 (4)	11 (10)
Nakaguchi, 2001 [20]	106	82:24	67	63 (28)	-	-	-	17 (16)
Oishi, 2001 [38]	116	84:32	72	100 (86)	-	-	11 (9)	10 (9)

OAC = oral anticoagulation; PAI = platelet aggregation inhibitor; reCSDH = CSDH recurrence
[a]: Four patients died before discharge, therefor analyses were performed in 457 patients.
[b]: Two patients died before discharge, therefor analyses were performed in 246 patients.
[c]: Because of rounding, percentages in combined "OAC or PAI" group may differ with one percent from the sum of "OAC" and "PAI"

female ratio was 3:1 with a mean age of 68.9 years (SD 4.1; n = 18 studies) and a precipitating head trauma in 2089 patients (62.6%; n = 17 studies). Fourteen hundred and thirty-eight patients had used anti-thrombotic agents (28.9%; n = 17 studies) with the use of anticoagulation in 517 (10.4%, n = 11 studies), platelet aggregation inhibitors (PAI) in 829 (18.1%, n = 10), and unspecified therapy in 92 patients (2.0%, n = 5 studies). All patients were treated by BHC with subdural drainage during 24 to 72 h (table 4).

Imaging findings: hematoma laterality, thickness, and midline shift

Nineteen studies reported on uni- and bilaterality with incomplete data in two [43, 44], resulting in seventeen studies with a total of 4400 patients for laterality analysis with a high study heterogeneity (I2 = 70%). Patients with bilateral CSDH had higher hematoma recurrence than patients with a unilateral CSDH, although not reaching significance (figure 3a, RR 1.34, 95% CI 0.98–1.84).

Six studies with a total of 2150 patients reported on hematoma thickness using a cutoff value of 15 (n = 1), 20 (n = 4), or 25 (n = 1) mm. The largest group comparison showed that the recurrence rate of patients with a CSDH thickness of more than 20 mm was higher than patients with a hematoma thickness of less than 20 mm (Figure 3b, RR 1.38, 95% CI 1.11– 1.73). Adding the studies with cut off values of 15 or 25 mm, a similar result was seen (combined group: RR 1.46, 95% CI 1.19–1.79). Study heterogeneity was low in both comparisons (I2 = 21% and I2 = 5% respectively).

Thirteen studies with a total of 2874 patients described midline shift employing a cutoff value of 5 (n = 1), 10 (n = 8), or 15 mm (n = 1) or reported only on the presence or absence of midline shift (n = 3). Patients with a midline shift more than 10 mm had a higher recurrence rate than patients with a midline shift below 10 mm (Figure 3c, RR 1.79, 95% CI 1.45–2.21). For the combined midline shift groups (adding results of 5 mm and 15 mm to 10 mm), recurrence risk remained significantly higher (RR 1.76, 95% CI 1.45–2.14). In the three studies describing only absence or presence of midline shift, there was no difference between the groups (RR 0.82, 95% CI 0.39–1.72). Study heterogeneity was low in all three comparisons (I2 = 32%, I2 = 14%, and I2 = 0 respectively).

Imaging findings: hematoma density and architecture

Seventeen studies with a total of 3813 patients reported on hematoma density. In fifteen studies (n = 3614), data were reported or could be reconstructed on homogeneity of the hematoma and mixed density categories. There was a higher

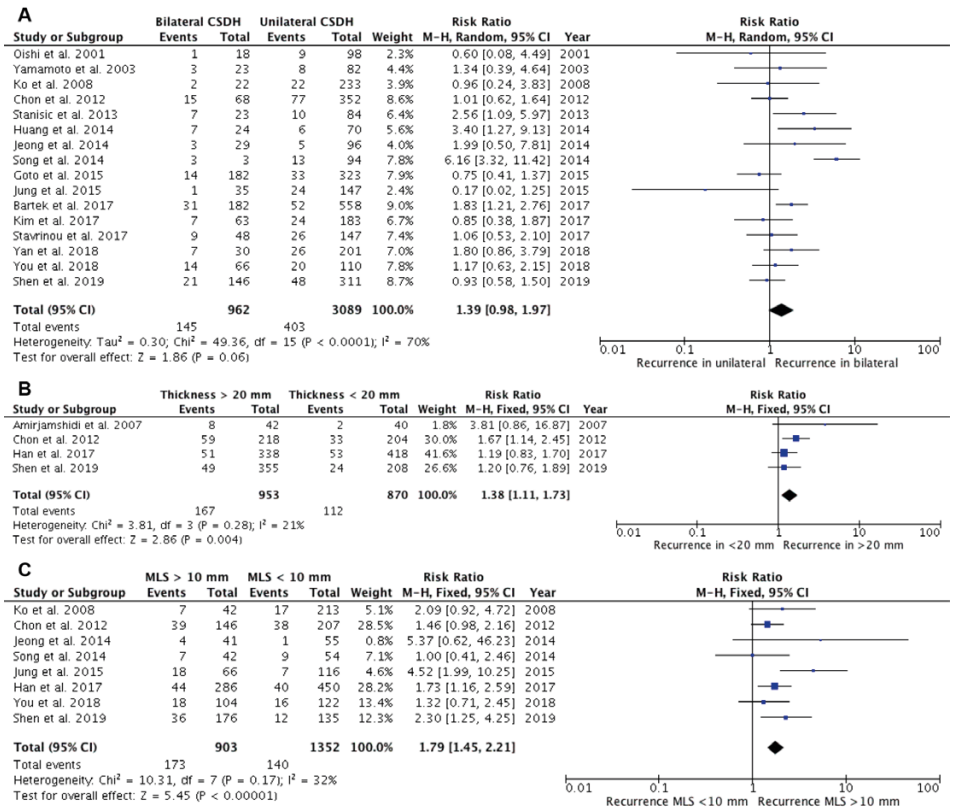

Figure 3. Forest plot on CSDH recurrence. A. uni-versus bilateral hematoma; B. hematoma thickness < or > 20 mm C. midlineshift < or > 10mm.

risk of recurrence in patients with a mixed density hematoma than in patients with a (complete hypo-, iso-, or hyperdense) homogeneous hematoma (figure 4a, RR 1.64, 95% CI 1.14–2.37). Eleven studies reported on homogeneous iso- and hypodensity versus hyper- and total mixed density hematomas. Patients with hyper- and mixed density hematomas had more often CSDH recurrence than patients with homogeneous hypo- and iso-density hematomas (figure 4b, RR 2.38, 95% CI 1.69–4.73). Study heterogeneity was high in both comparisons (I2 = 74% and I2 = 71% respectively).

Nine studies with a total of 1965 CSDH patients reported on hematoma architecture by evaluation of all four predefined categories. Patients with laminar or separated architecture had a higher risk of hematoma recurrence than those with hematomas in which these features were not present (figure 5a,

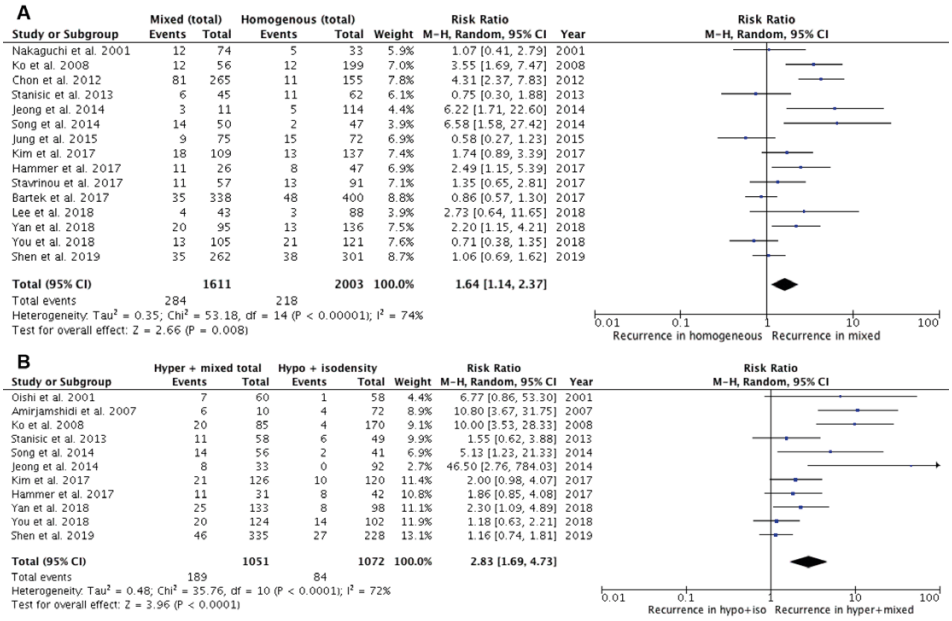

Figure 4. Forest plot on CSDH recurrence. A: homogeneous versus mixed density hematoma; B: iso- and hypodensity versus hyper- and mixed density hematoma

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RR 1.37, 95% CI 1.04–1.80; and figure 5b, RR 1.76, CI 95% 1.38– 2.16, respectively). Study heterogeneity was low in both comparisons (I2 = 0 and I2 = 43 respectively). There was no difference in hematoma recurrence for trabecular architecture (RR 0.88, 95% CI 0.52–1.49), with high study heterogeneity (I2 = 61%).

Imaging findings: hematoma volume and MRI- sequences

One study (n = 514) reported on hematoma volume with frequencies above or below a prespecified cut off value of 121 mm3 based on the receiver operating characteristics (ROC) curve, with the highest recurrence rates in hematomas with a baseline volume above 121 mm3 [28]. Two studies described results on MRI-sequences in relation to CSDH recurrence. The first study (n = 414) reported data on the predictive value of MRI-T1 and -T2 sequences, revealing the T1 classification to be the only prognostic predictor for CSDH recurrence in T1-iso/hypo-intensity group relative to the T1-hyperintensity group [47]. The second study (n = 131) revealed more CSDH recurrence when baseline MRI showed DWI hyperintensity compared to hypo-intensity [44].

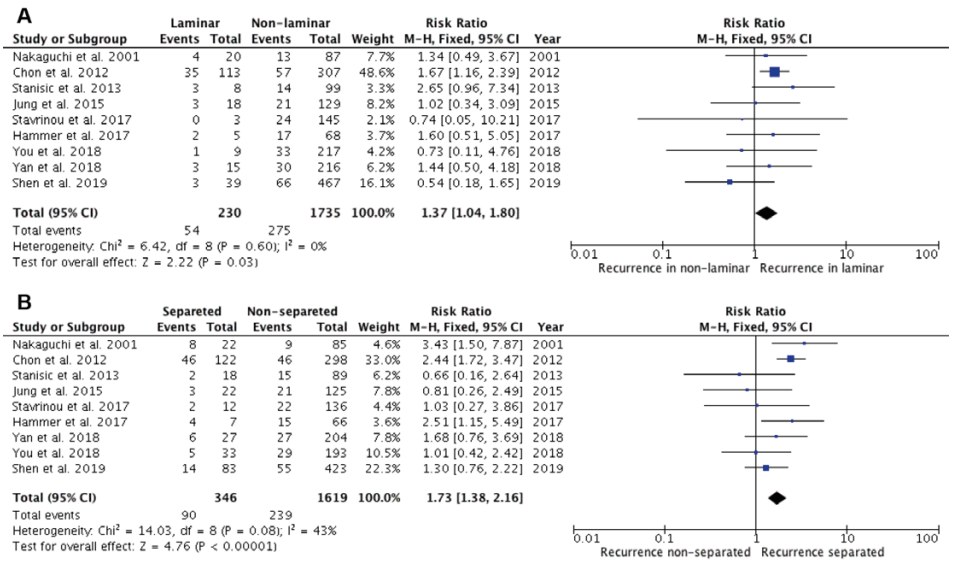

Figure 5. Forest plot on CSDH recurrence. A: laminar hematoma architecture; B: separated hematoma architecture

Discussion

In this meta-analysis including over 5500 patients, we identified prognostic factors on CT for recurrence of surgically treated CSDH patients. Hyperdense and mixed density hematoma were associated with the highest risk of CSDH recurrence, as were laminar and separated architecture hematomas. In addition, CSDH with greater magnitude of hematoma thickness and midlines shift carried an increased risk for recurrence.

The establishment of radiological prognostic factors for CSDH recurrence is of importance in the identification of vulnerable symptomatic CSDH patients for poor outcome and retreatment [19, 20]. This population would benefit most from optimization of therapy. Many preoperative radiological parameters have been reported as prognostic factors for CSDH recurrence, but results are conflicting [21–34, 51].

Overall, we found homogeneous hyperdense and mixed density hematoma to be associated with increased recurrence rates. Hematoma density relative to brain parenchyma on a CT image represents the proportion of fresh blood, with hypodense areas representing hematoma of older age and hyperdense

components of more recent or active bleeding [52–55]. This imaging appearance reflects the protein concentration from plasma exudation with higher concentration in hyperdense hematoma [26, 38, 50, 56, 57]. In experimental studies, blood evokes an inflammatory reaction in the subdural space [42, 58]. This inflammatory reaction is associated with a high amount of inflammatory markers and causes the CSDH to be more active and is presumed to play a part in hematoma persistence, a greater tendency for re-bleeding and recurrence [39, 58–61]. Novel experimental approaches have evaluated pharmacological adaption of endothelial barrier function, modifying endothelial permeability and plasma exudation [62, 63]. However, reproducible animal models of human CSDH are not established yet [42]. Results of this meta-analysis are in concordance with the abovementioned pathophysiology of protein concentration in the subdural space, which also explains why lower recurrence rates were found in iso- and hypodense CSDH than in hyperdense hematomas.

Besides categories that describe density of the hematoma, internal architecture types are also used for classification. An established and commonly used classification is that of Nakaguchi (homogeneous, laminar, separated, trabecular), corresponding to proposed stages in natural history of a CSDH [26]. Overall, we found a higher recurrence risk in laminar and separated hematoma than in other hematomas. Several individual studies, however, did not report a high recurrence rate in laminar hematoma [29, 43, 64], but did report trabecular hematoma, corresponding to hematoma with multiplicity of cavities, to reoccur more often [49, 65–69]. This variation and discrepancy are most likely caused by the many available architecture categories which are applied parallel to the classification of Nakaguchi (i.e., loculated hematoma, hematoma with multiplicity of cavities, layered type hematoma, organized hematoma, and niveau formation), but could also be due to difficulties in applying the classification correctly [18, 26, 45, 59, 70, 71]. In addition, complex internal architecture categories might be very informative, but application can lead to significant intra- and interobserver variability compromising generalizability. In this paper, we propose and demonstrate the benefit of a simplified hematoma classification system based on hematoma density solely. This comprises of a homogeneous iso- and hypodensity category and a second category of CSDH with hyperdense components. This simplified classification could be easy to apply in daily practice with presumably low inter- and intra-observer variation and good insight in the recurrence risk. Future research should confirm the significance of this finding, and also whether adding the different architecture subcategories yields valuable surplus information.

We demonstrate that a greater magnitude of hematoma thickness and a midline shift is associated with an increased recurrence risk. Increased CSDH size and midline shift are often attributed to brain atrophy in close relation to aging, providing the CSDH a potential space to increase easily [37, 40]. Previous studies have shown cerebral atrophy to be a potential risk factor for CSDH recurrence [20, 50]. The intracranial (counter-) pressure from brain volume reflects the elasticity of brain parenchyma and may play a part in optimal hematoma absorption [40, 41]. Due to a decrease in brain elasticity and counter pressure by advanced age and atrophy post-operative, re-expansion might potentially be less effective leaving a larger postoperative subdural space that could facilitate persistence or recurrence of CSDH [23, 41, 72]. This mechanism may also explain the increased recurrence in bilateral CSDH. In daily practice, grading of cerebral atrophy is a challenging and difficult task at the time of CSDH diagnosis. The compression caused by the subdural hematoma on the involved hemisphere distorts the gyri sulci pattern due to the raised intracranial pressure and complicates a reliable assessment. Furthermore, several scales exist to classify atrophy, causing once again large inter-and intra-observer variation. Further evaluation of this parameter was therefore beyond the scope of this meta-analysis. Recurrence risk is influenced by patient as well as radiological hematoma characteristics. Since a non-contrast CT scan is the most frequently performed diagnostic modality, evaluation of CT predictors is of great additional value next to other presumed clinical predictors such as age, concomitant chronic illness or coagulopathy [21, 23, 28, 64, 71, 73–75]. Similar to the limitations of studies evaluating the value of radiological predictors in recurrence risk, varying results have also been published regarding the effect of age, sex, anti-coagulant use, and chronic illness [33, 72, 76, 77]. The addition of radiological predictors of recurrences to baseline patient characteristics for risk calculation may facilitate clinicians to identify patients prone to recurrence more accurately. These findings could lead to adaptation of treatment measures on an individual basis in order to lower the recurrence risk, for example by postponing surgical drainage when hyperdense components are present or adjusting the (local standard) term for anti-coagulant therapy resumption post-operative. Limited data also suggest that the addition of corticosteroids might be beneficial in reducing recurrence risk in high-risk patients [73].

Limitations of this meta-analysis are due to methodological aspects of the included studies. We encountered significant heterogeneity in the definitions used for CSDH recurrence, i.e., only radiological recurrence, or the combination of recuring symptoms with radiological persistence or progression of CSDH,

or merely re-operation without clarifying the criteria for reoperation. Furthermore, differences in duration of follow-up, hematoma density, and architecture classification and measurement techniques for radiological parameters also contributed to data heterogeneity. Evaluation of study quality using the NOS questionnaire revealed that the majority of studies did not reach maximum quality scores, mainly because no adjustments were performed for confounding factors and incomplete follow up information. However, the findings were generally consistent and in line with acknowledged clinically relevant parameters.

For the present study, we included only surgically treated CSDH patients by burr hole or twist drill craniostomy with subdural drainage, the mainstay treatment worldwide, in order to eliminate the potential effect of different treatment strategies on recurrence rates. We maintained a study protocol with strict inclusion and exclusion criteria in order to achieve good quality and homogeneous data as good as possible, which to our knowledge has provided the first data review on this subject.

Conclusion

From the present meta-analysis, we have derived several CT predictors that are associated with recurrence after surgical treatment of CSDH. In particular, CSDH with hyperdense components or with laminar or separated architecture type entail higher recurrence rates. Preoperative assessment of these parameters identifies a population with higher CSDH recurrence risk, and appreciation of these findings allows clinicians to apply an individualized management strategy.

Future research is necessary to validate the prognostic value of these CT parameters in prospective studies and in particular investigate the value of a simplified density classification. Clear definitions and description of radiological measurement techniques are mandatory for a reliable evaluation.

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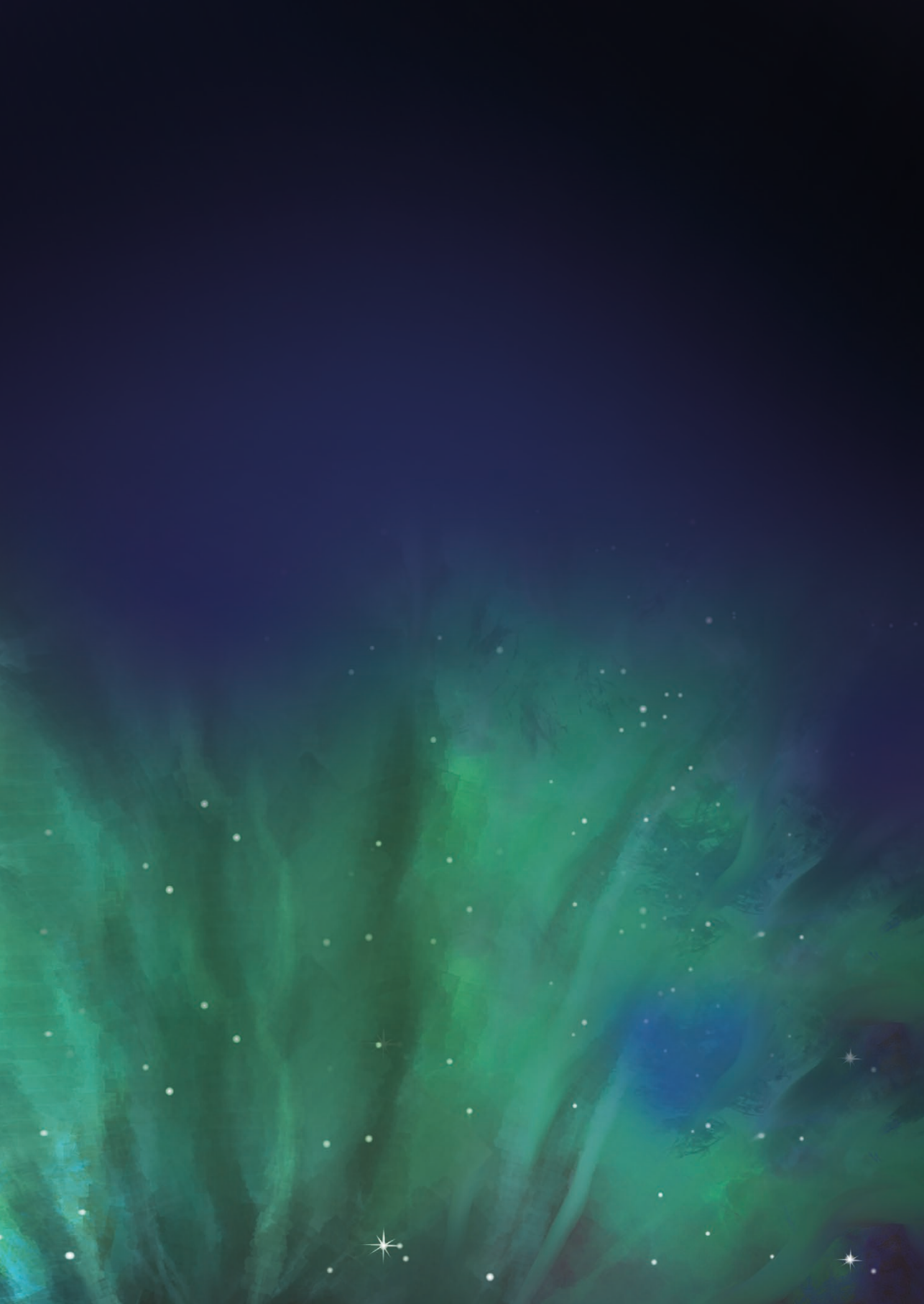

6

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

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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

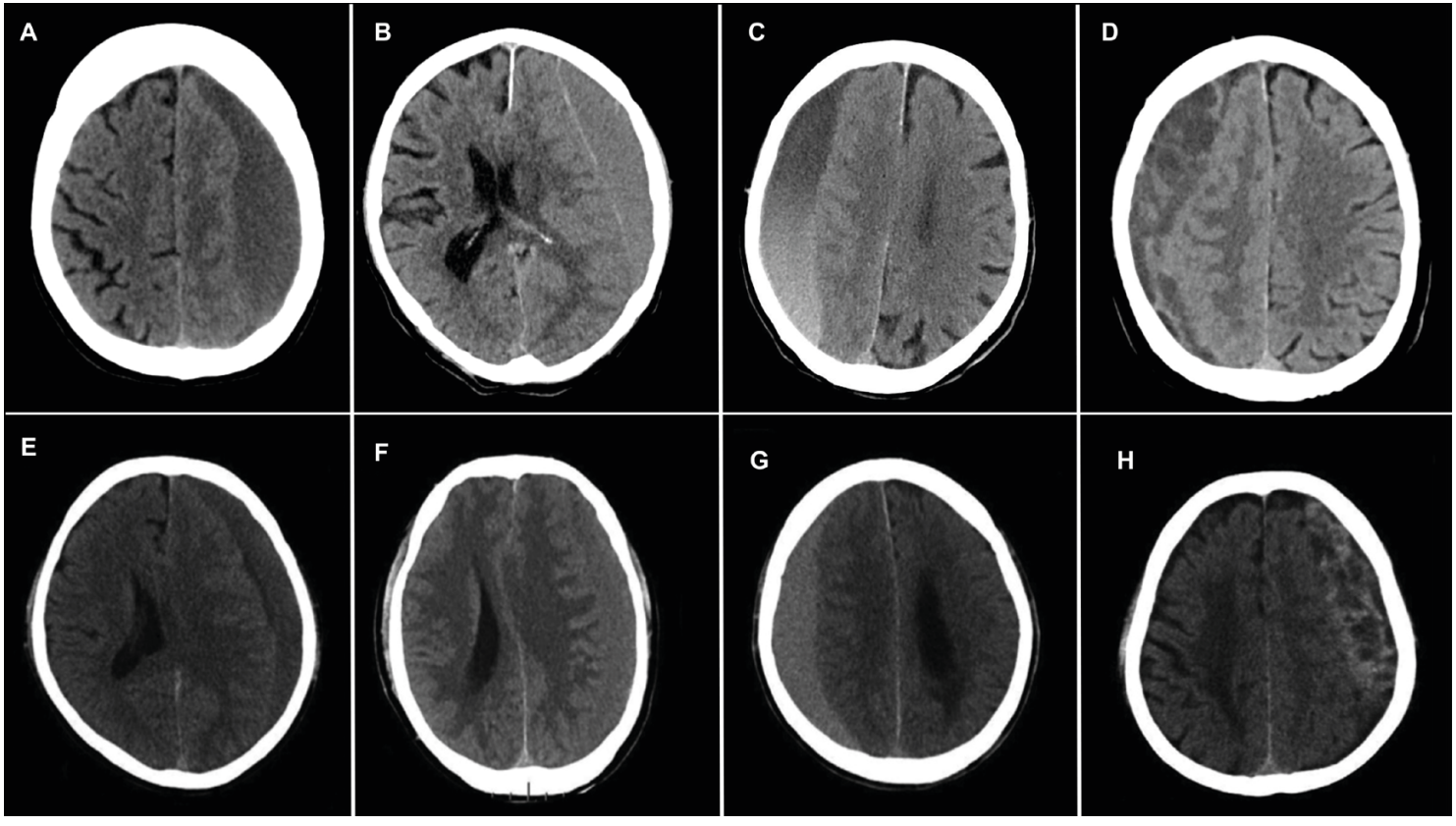

Figure 1. Radiological hematoma subtypes by architecture and density. A: homogeneous architecture (hypodense case); B: laminar architecture; C: separated architecture; D: trabecular architecture; E: homogeneous hypodense density; F: homogeneous isodense density; G: homogeneous hyperdense density; H: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

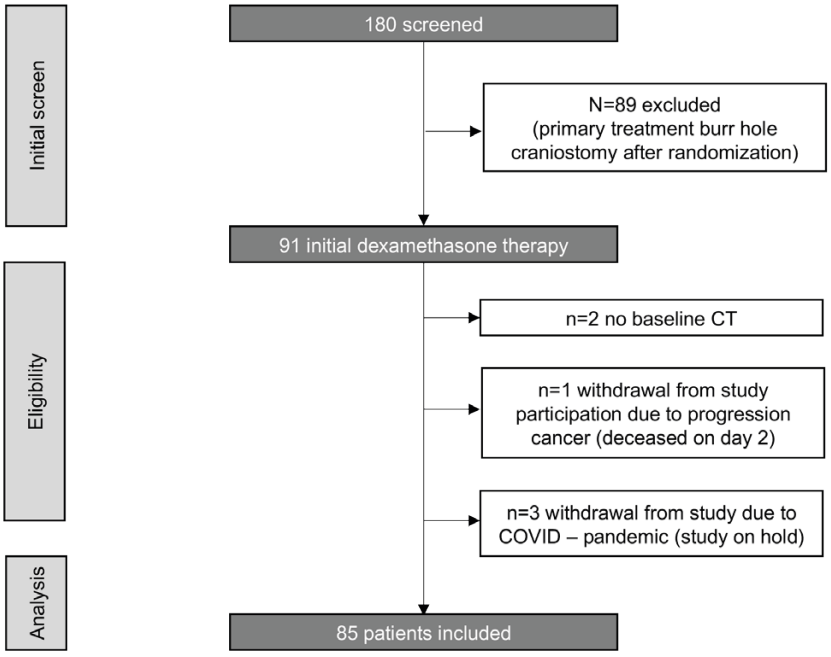

Figure 2. CONSORT flowchart of patient inclusion.

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).

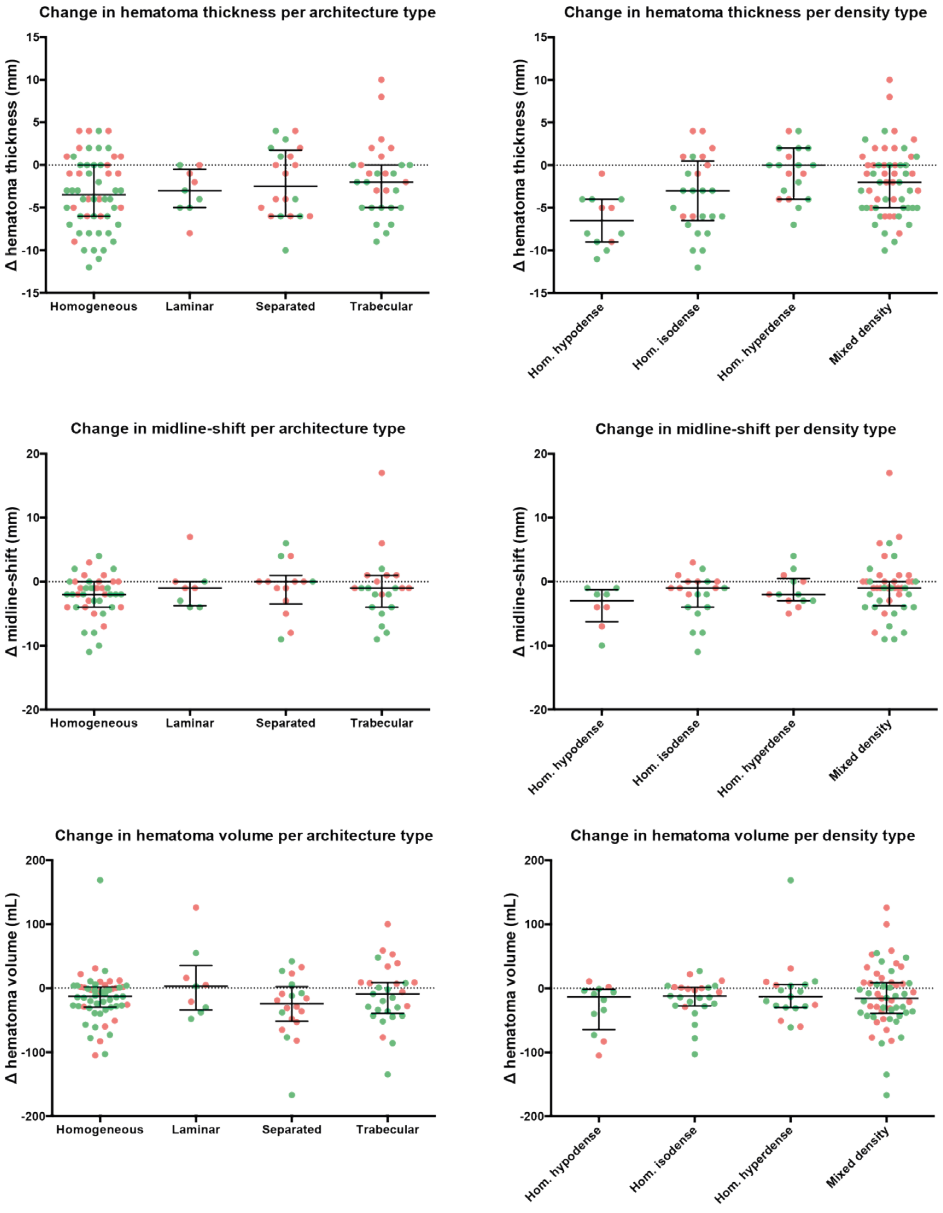

Figure 3. Boxplot of change in radiological parameter per hematoma subtype. Green dot: successful on dexamethasone monotherapy; Red dot: additional surgery required.

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).

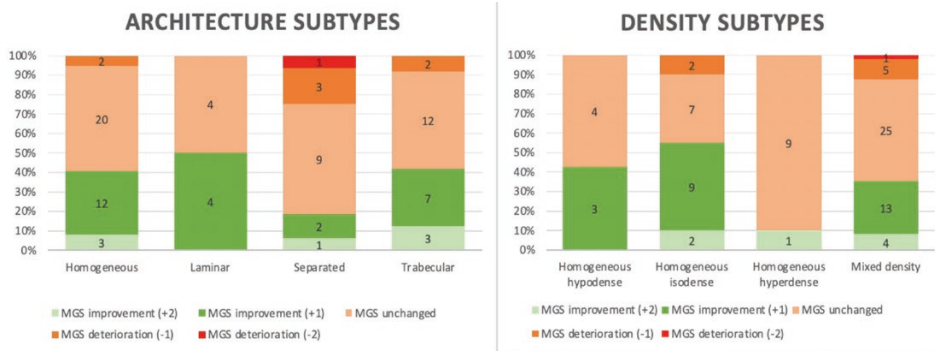

Figure 4. Change in symptom severity by hematoma subtypes – at two weeks. MGS = Markwalder Grading Scale score. Numbers in chart indicate total number of patients with specific change in MGS-score (improvement, no change, deterioration).

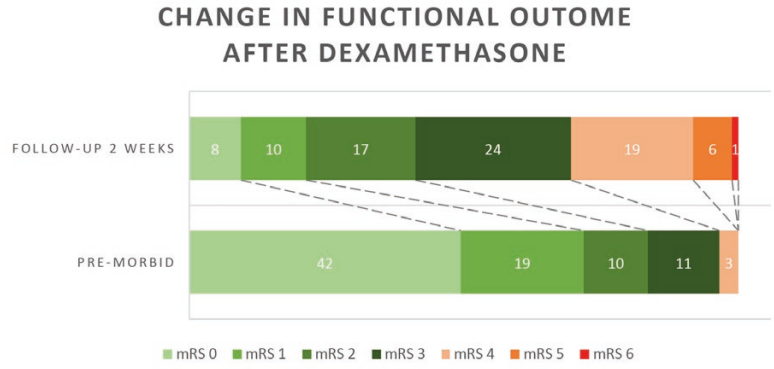

Figure 5. Change in functional outcome (modified Rankin Scale) – at two weeks. mRS = modified Rankin Scale score. Numbers indicate total number of patients with specific mRS-score.

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

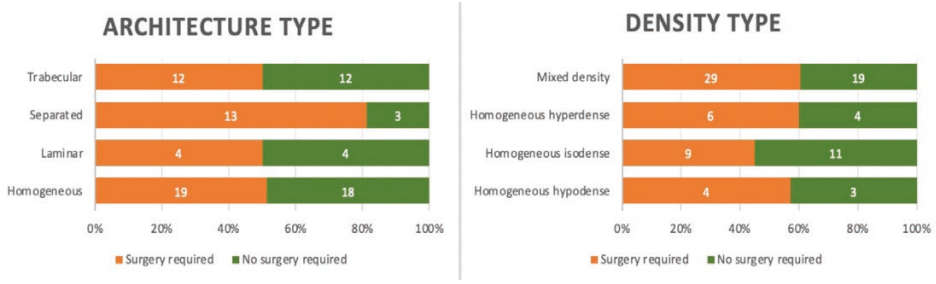

Figure 6. Need for additional surgery after dexamethasone therapy – by hematoma subtypes. Numbers indicate total number of patients requiring surgery (orange) or succeeded without surgery (green).

(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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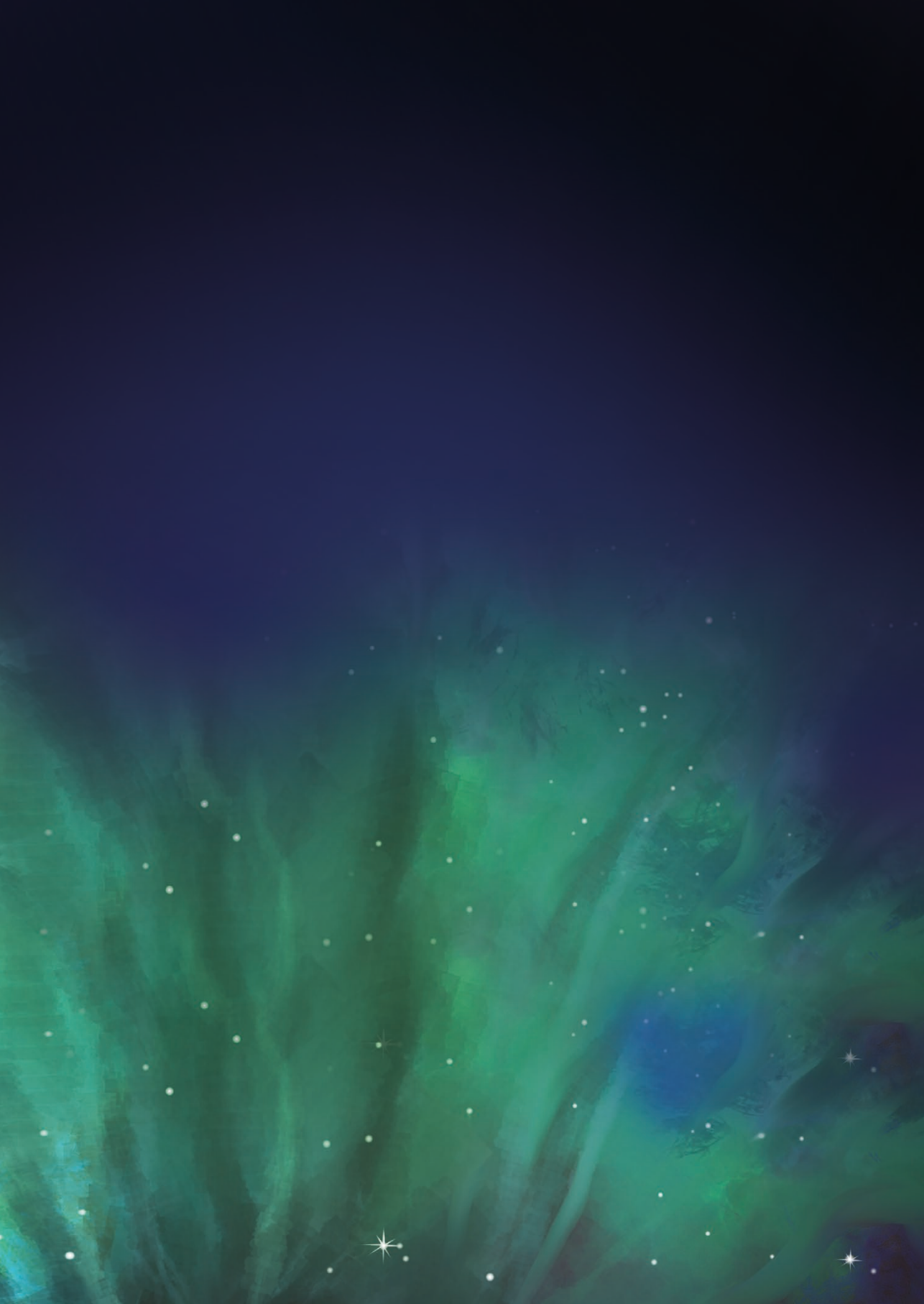

7

Summary, general discussion and future perspectives

Summary

In this thesis, the management of symptomatic chronic subdural hematoma is explored. We have focused on the comparison of therapeutic options and optimization of treatment by an in-depth look into diagnostic approach. In the first part of this thesis, the two main treatment options were compared: dexamethasone therapy versus surgery. In the second part the prognostic value of baseline computed tomography (CT-) parameters on treatment outcome was evaluated.

In **chapter 2** the efficacy and safety of initial dexamethasone therapy and primary surgery by burr hole craniostomy for symptomatic chronic subdural hematoma patients was evaluated. Data was retrospectively collected from consecutive patients treated in two large neurosurgical centers, each having their own specific treatment regimen. Superiority of surgery was hypothesized by assuming an achievement of a good functional outcome as expressed by a modified Rankin Scale score of 0-3, in 80% of patients treated with surgery versus 60% after dexamethasone monotherapy.

In total 60 patients were included in cohort A in whom surgery by burr hole craniostomy was performed with two days subdural drainage. In cohort B also 60 patients were included, receiving dexamethasone therapy in a dosing regimen of 6 or 8 mg daily during an undefined period. Both patient groups showed similar baseline characteristics, including symptom severity, use of antithrombotic therapy and radiologic hematoma size.

At three months no significant difference in functional outcome or symptom severity was found between both groups. A favorable modified Rankin Scale (mRS) score (0–3) and Markwalder Grading Scale (MGS) score (0-1) was observed in 70% and 96% of patients in the surgical cohort and 76% and 96% in the dexamethasone cohort respectively (adjusted odds ratio [aOR] for favorable mRS 0.77, 95% CI, 0.30–1.98; aOR for favorable MGS 0.98, 95% CI, 0.45–2.15). Additional surgery was performed in 83% of patients receiving dexamethasone therapy, with a median duration to surgery of 6 days. Compared with the dexamethasone cohort, a significantly lower complication rate (35% versus 55%; aOR 0.42, 95% CI 0.20–0.89) and shorter duration of hospitalization (5 days versus 10 days; aOR 0.04, 95% CI 0.00–0.66) was observed in the surgical cohort. Mortality at 6 months was 10% in both groups (OR 1.04, 95% CI 0.29–3.76). A more intensive radiological monitoring was required after initial

dexamethasone therapy with 85% of patients receiving ≥1 follow-up CT scans in the dexamethasone cohort against 48% in the surgical cohort (OR 6.16, 95% CI 2.53–14.95). Interestingly, hematoma recurrence was higher in patients after primary surgery (22%) compared to initial dexamethasone therapy (12%; aOR 2.11, 95% CI 0.77–5.79). In addition, a higher re-operation rate was observed in the surgical cohort compared to the dexamethasone cohort (18% versus 6%).

Overall, we concluded that dexamethasone therapy was associated with a high rate of crossover to surgery, significantly longer overall hospital stay, more intensive radiological monitoring and more complications compared to primary surgery. Whether the lower hematoma recurrence rate and reoperation rate were related to prior dexamethasone therapy, requires further investigation.

Chapter 3 describes the protocol for the DECSA-trial. The DECSA-trial was a multicenter, randomized controlled trial (RCT) with a blinded endpoint assessment. The primary objective of the trial was to evaluate non-inferiority of dexamethasone to surgery by burr hole craniostomy on functional outcome as expressed by the modified Rankin Scale score at three months in symptomatic chronic subdural hematoma patients. Patients in the intervention arm received dexamethasone therapy in a fixed dosing regimen with a daily dose of 16 mg (8 mg every 12 hours) on day 1 to 4. Thereafter, dexamethasone was tapered by half every three days until a dosage of 0.5 mg a day on day 19 and stopped on day 20. The reference treatment was an operation by burr hole craniostomy with two days subdural drainage. We aimed to include 420 patients to show non-inferiority of dexamethasone therapy with a power of 90%, assuming that the true effect of dexamethasone had an OR 1.15 for a better functional outcome on the modified Rankin Scale. The limit for inferiority was set at an OR of < 0.9.

In **chapter 4** the results of the DECSA-trial are presented. The trial was prematurely halted at the first interim analysis after review by the data and safety monitoring board in February 2021. The interim analysis included the first 150 patients and was extended to the actual number of 252 included patients for additional review. Termination of the trial was recommended because of safety concerns. Hence, the primary outcome (60% of the planned 420) was assessed in 252 patients recruited from 12 hospitals.

A total of 127 patients were randomized to dexamethasone therapy and 125 patients to surgery. Dexamethasone treatment scheme of 19-days was completed in 59% of patients. During the study period 61% of the dexamethasone group

required additional treatment, which consisted of additional surgery in 56% and a second dexamethasone scheme in 5%. Additional treatment was performed after a median duration of 20 days dexamethasone. In the surgical group additional therapy was applied in 17%, consisting of dexamethasone treatment in 10.4% and a reoperation in 6.4%.

At three months fewer patients in the dexamethasone group had a favorable functional outcome (modified Rankin Scale score 0-2) than in the surgery group; 102 of 124 patients (82.3%) and 110 of 124 (88.7%) respectively. The adjusted common odds ratio (acOR) for a worse functional outcome (modified Rankin Scale score) associated with dexamethasone therapy at three months was 2.28 (95% CI, 1.43 to 3.64). More complications were observed in the dexamethasone group compared to the surgical group (67% versus 33%). 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% respectively. 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. Mortality was observed in 6% in dexamethasone and 2% in surgical group (aOR 2.63, 95% CI 0.43 to 16.67).

Based on the results of this trial, we concluded that 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 hospital stay. The results showed there is no indication for dexamethasone therapy in symptomatic patients with chronic subdural hematoma.

In **chapter 5** we systematically reviewed studies on prognostic radiological parameters for chronic subdural hematoma recurrence after surgical treatment. CT parameters of interest included: hematoma laterality, thickness, midline shift, volume, and hematoma appearance subtype. Radiological appearance was described by categorization of hematoma into the following four density subtypes: 1. homogeneous hypodense, 2. -iso-dense, 3. -hyperdense and 4. mixed density; and also the four architectural subtypes as described by Nakaguchi: 5. homogeneous (total), 6. laminar, 7. separated and 8. trabecular.

After screening 3112 publications, we were able to include 22 cohort studies that fulfilled the in- and exclusion criteria for study selection after searching

electronic databases until September 2020. Study quality appeared fair to poor, mainly due to the lack of adjustments for confounding factors. A total of 5566 symptomatic chronic subdural hematoma patients were included in this systematic review with recurrence occurring in 801 (14.4%) patients.

We found baseline hematoma appearance by density subtypes to be the strongest radiological prognostic factor of chronic subdural hematoma recurrence after surgery. Hematoma with hyperdense components, which included the density subtypes hyperdense homogeneous and mixed density hematoma, showed the highest recurrence rates (pooled risk ratio [RR] 2.83, 95% CI 1.69–4.73), followed by the laminar (RR 1.37, 95% CI 1.04–1.80) and separated architecture subtypes (RR 1.76, 95% CI 1.38–2.16). Hematoma thickness and midline shift above predefined cut-off values (10 mm and 20 mm) were also associated with an increased recurrence rate (RR 1.79, 95% CI 1.45–2.21 and RR 1.38, 95% CI 1.11–1.73, respectively).

Thus, after application of radiological parameters for the risk assessment for treatment failure, we found hematoma with hyperdense components to be the strongest prognostic factor of chronic subdural hematoma recurrence after surgery. These findings potentially allow patient-specific risk assessment and might prompt tailored treatment.

In **chapter 6** we focused on the prognostic value of radiological hematoma subtypes in symptomatic patients with chronic subdural hematoma treated with dexamethasone. The aim of this study was to explore whether the response to dexamethasone therapy differed in the various radiological hematoma subtypes. The primary outcome was reduction in hematoma size and clinical improvement after two weeks of dexamethasone treatment. Hematoma subtypes were classified into four density (homogeneous hypodense, -iso-dense, -hyperdense and mixed density) and four architectural subtypes (homogeneous, laminar, separated and trabecular). Hematoma reduction was assessed by measuring the change in hematoma thickness, midline shift and hematoma volume. Clinical improvement was evaluated by measuring the change in symptom severity using the Markwalder Grading Scale score.

In total 85 patients were included from the three participating neurosurgical centers with 114 chronic subdural hematoma. The largest reduction in radiological parameters was observed in homogeneous hypodense hematoma, with mean changes in hematoma thickness, midline shift and volume after

dexamethasone therapy of -7 mm (SD 3), -4 mm (SD 3) and -30 mL (SD 38) respectively. We performed a multiple linear regression analysis to quantify hematoma reduction after dexamethasone, adjusting for age, sex and baseline value of the radiological parameter. This demonstrated the largest reduction in hematoma thickness in homogeneous hypodense hematoma, compared to homogeneous iso-dense (regression coefficient b -3.8 mm, 95% CI -7.0 to -0.5), homogeneous hyperdense (b -5.5 mm, 95% CI -9.0 to -2.1), and mixed density hematoma (b -4.5 mm, 95% CI -7.5 to -1.5). The combined density analysis also showed a significantly larger decrease in hematoma thickness in hematoma without hyperdense components (homogeneous hypo- and –iso-density hematoma) compared to hematoma with hyperdense components (homogeneous hyperdense and mixed density hematoma; adj. b -2.2 mm, 95% CI -4.1 to -0.3). A significant larger change in midline shift was also found in hematoma without hyperdense components compared to hematoma with hyperdense components (adj. b -1.3 mm, 95% CI -2.7 to 0.0). No significant differences were found between the different radiological subtypes and hematoma volume.

Between the eight hematoma subtypes, clinical improvement expressed by an improvement in Markwalder Grading Scale score was higher in patients with chronic subdural hematoma without hyperdense components (52%) compared to hematoma comprising hyperdense components (31%). Lowest rate in improvement was seen in patients with homogeneous hyperdense hematoma (10%) and hematoma with separated architecture type (19%). Regression analysis showed chronic subdural hematoma with a homogeneous hyperdense subtype to be a significant predictor of no neurological improvement (OR 0.08, 95% CI 0.0-0.8) compared with homogeneous hypodense hematoma. Due to persistence or deterioration of symptoms and radiological status, we observed the need for additional surgery at two weeks in 54% of dexamethasone-treated patients, with the highest rate in separated hematoma (80%).

In conclusion, the largest reduction in hematoma size was achieved in symptomatic patients with chronic subdural hematoma without hyperdense components after two weeks of dexamethasone treatment. 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.

General discussion

Optimal management of symptomatic patients with chronic subdural hematoma is a continuing clinical challenge. Throughout the years the effectiveness and safety of different surgical techniques have been subjected to many trials [1]. Both twist-drill and burr hole craniostomy with subdural drainage have been demonstrated to be highly effective surgical procedures [2,3]. However, the demand for a less invasive approach persisted while surgery might not always be the preferred treatment for this generally vulnerable, older patient population. In contrast to the many randomized surgical trials, only a few studies have been conducted to date that examined the effectiveness of surgery compared to a conservative therapy [4-16]. In the search for more clarity on the role of corticosteroids in the treatment of chronic subdural hematoma, eight randomized trials have been initiated in the past ten years of which the greater majority is still ongoing [9,11, 17-22]. Meanwhile dexamethasone has become a widely accepted alternative therapy in symptomatic chronic subdural hematoma patients, administered either as stand-alone therapy or as additional treatment to surgery.

With the studies performed in this thesis, our aim is to provide an answer to the question whether dexamethasone is an appropriate alternative to surgical treatment for symptomatic patients. Furthermore, we have explored which radiological variables are of prognostic value for treatment outcome.

Dexamethasone as alternative to surgery

Functional outcome

Based on the studies in this thesis, we conclude that there is no beneficial effect of dexamethasone on functional outcome compared to surgery in symptomatic patients with chronic subdural hematoma [23,24]. We observed a significantly worse functional outcome, expressed by the modified Rankin Scale (mRS) score, and more complications at three months in patients receiving dexamethasone therapy compared to surgery in our randomized controlled trial. Moreover, to achieve the requested favorable functional outcome, an additional treatment was required in 61% of patients in the dexamethasone group compared to 17% in the surgical group. With respect to our study hypothesis, we could not detect non-inferiority of dexamethasone compared to surgery, given the results of the interim-analysis. In the adjusted analyses surgery could even be regarded as a superior treatment option [24].

In our DECSA-R cohort study we evaluated the effects of dexamethasone versus surgery in two similar and symptomatic patient cohorts. We observed similar results on functional outcome between both groups. However, a much higher crossover rate in the dexamethasone group compared to surgery of 86% was reported to achieve a favorable functional outcome. This effectively resulted in the comparison of two surgical groups and could explain the similarities in functional outcome. The observed complication rate in the DECSA-R study was much higher in the dexamethasone group compared to surgery, which we also found in our randomized trial [23].

While previous cohort studies suggested equal or even better functional outcome after dexamethasone therapy [4-8, 10], the disappointing effect of dexamethasone we observed is in accordance with results of two recent randomized trials [9,11]. A rather small pilot study in twenty patients evaluated the effectiveness of dexamethasone therapy versus placebo. The success rate of dexamethasone therapy was 60% (6/10) against 70% (7/10) in the placebo group and did not differ significantly between both groups, while higher adverse events were seen in the dexamethasone group. A second, more recent trial (DEX-CSDH) compared the effect of dexamethasone therapy as add-on treatment prior to surgery with surgery alone in a large surgical cohort of 748 patients [9,11]. In the DEX-CSDH trial pre-operative treatment with dexamethasone resulted in significantly fewer favorable outcomes (84% versus 90%) and more adverse events (17% versus 10%) compared to surgery alone at 6 months [11].
There are several reasons for the discrepancy between the older cohort studies and the recent trials. There was a difference in definitions between studies for good functional outcome, as well as an important allocation bias of treatment in the non-randomized studies. Heterogeneous allocation likely resulted in the administration of dexamethasone therapy in mildly affected patients and surgery in the more severely affected patients. Furthermore, due to methodological issues the registration of clinically relevant parameters such as complications and duration of hospital stay have not been performed or might have been sub-optimally recorded.

Possibly a higher symptom severity limited the beneficial effects of dexamethasone in the DECSA-trial since 73% of patients in the dexamethasone group had a baseline Markwalder Grading Scale score of 2 compared to 52% in de surgical group. Premorbid functional performance was also worse in the dexamethasone group compared to the surgical group; a modified Rankin Scale score of 3 to 5 in 17% versus 10% respectively. Therefore, we corrected for the

pre-morbid modified Rankin Scale score in the adjusted analyses. Functional outcome was still worse at three months in the dexamethasone treated patients. To explore whether more benefit was gained on dexamethasone therapy in mildly symptomatic patients, subgroup analyses were performed. A compromised efficacy of dexamethasone compared to surgery on functional outcome persisted in both mildly as well as severely symptomatic patients. In the dexamethasone group recovery to pre-morbid modified Rankin Scale score at three months was achieved in 42% (13/30) of patients with baseline Markwalder Grading Scale score of 1, compared to 31% (28/90) in patients with a baseline Markwalder Grading Scale score of 2. In the surgical group a functional recovery to pre-morbid modified Rankin scale score was achieved in 55% (30/55) and 44% (23/52) of patients with baseline Markwalder Grading Scale score of 1 and 2 respectively. As expected, functional recovery is worse in severely affected patients in both treatment arms. Due to the small numbers however, no firm conclusions can be drawn.

Complications

In our randomized trial as well as the DECSA-R cohort study more complications were observed in the dexamethasone treated patients. This is another strong argument not to administer dexamethasone in symptomatic chronic subdural hematoma patients. Consistent with the results of the recently published DEX-CSDH trial, we found a higher rate of infections, hyperglycemia and delirium in dexamethasone treated patients compared to surgery in our trial [11, 24]. The complications are mainly related to the known side-effects of dexamethasone [25]. Dexamethasone dosing scheme was quite similar in both trials. Previous cohort studies also reported mainly hyperglycemia and infections to occur in dexamethasone treated patients [6-8]. Remarkably they did not reveal significantly more complications compared to surgery, while dexamethasone was administered in higher dosing schemes. This important discrepancy is most likely caused by the non-randomized study design.

Importantly, a slower onset of clinical improvement in dexamethasone treated patients compared to surgery increases the vulnerability of the elderly, hospitalized patient. Limited mobility increases the risk of in-hospital complications such as delirium, falls and systemic infections [26-28]. Furthermore, slower onset of clinical recovery, more complications and higher rate of additional hematoma treatment will cause prolonged hospital admissions. Consequently, the forementioned factors will likely result in

increased health care costs. Results of the DECSA trial regarding the effects on health care costs are expected to be published in the second quarter of 2022.

Radiological prognostic markers for treatment outcome

In daily clinical practice treatment strategies of patients with a chronic subdural hematoma are based on symptoms severity and radiological characteristics of the hematoma. In part 2 of this thesis, we evaluated whether treatment effects differ between the various radiological hematoma subgroups. Since CT imaging is the most frequently applied diagnostic modality in clinical practice, another focus of this thesis was to explore the prognostic value of baseline CT parameters on treatment outcome.

In our meta-analysis we evaluated the prognostic value of CT parameters to predict the likelihood of recurrence after surgery. The most prognostic variable was the classification of radiological hematoma subtypes. Hematoma with hyperdense components (homogeneous hyperdense and mixed density) showed the highest rate of chronic subdural hematoma recurrence or treatment failure in symptomatic patients after surgery, followed by separated and laminar architecture subtypes. As a next step we applied this radiological hematoma classification system in patients receiving dexamethasone therapy in our prospective CT-study as part of the DECSA study. The largest reduction in hematoma size was seen in hematoma without hyperdense components (homogeneous hypo- and iso-density hematoma). Furthermore, higher rates of treatment failure (persistence or recurrence of symptoms and hematoma) were observed in separated architecture type hematoma. In addition, this subtype together with homogeneous hyperdense hematoma showed less clinical improvement compared to other hematoma subtypes.

Taking into account the pathophysiological basis for chronic subdural hematoma formation, the presumed steady-state level of the inflammatory cascade in homogeneous hematoma subtype might explain the beneficial treatment effect of dexamethasone in this subtype [29-31]. Hematoma with hyperdense components represent a more recent and active bleeding with a higher inflammatory activity in the subdural space [31-44]. The laminar and separated hematoma subtypes have a hyper-fibrinolytic state with increased (premature) vascularity [45,32,33]. This might explain the higher recurrence rates observed after surgery, but also the worse radiological and clinical response with dexamethasone therapy.

Radiological parameters are scarcely reported in surgical studies, yet very diverse parameters have been mentioned as prognosticators [45-62]. Increased hematoma thickness, larger midline shift or hematoma volume and higher hematoma density than a pre-defined cut-off value, or the presence of bilateral chronic subdural hematoma are all reported as potential predictors for a worse treatment outcome. However, the clinical application and implementation of these results is challenging. First, it is difficult to determine which cut-off value should be used due to the different values applied in previous studies for hematoma size as well as Houndsfield Units for hematoma density [46,48,50-53,55,56,59-62]. Second, the large heterogeneity in study population as well as study design impede firm conclusions. Data quality was moderate to poor in most studies. Radiological parameters were seldom the focus of chronic subdural hematoma studies and only described as a secondary outcome lacking important details. Nevertheless, we believe that the meta-analysis, because of strictly applied in- and exclusion criteria, provides a reliable representation of the prognostic value of radiological hematoma subtypes for treatment outcome.

The use of radiological hematoma subtypes in daily clinical practice might therefore be useful in medical decision making. However, a framework with eight different hematoma subtypes complicates accurate classification. By simplifying the eight radiological subtypes into a dichotomized classification system as suggested, indicating hematoma with and without hyperdense components, the clinical implementation and use is simplified but still relevant. Given the results of our meta-analysis and prospective CT-study, more benefit in treatment outcome is achieved.

Conclusion

In this thesis we demonstrate that surgery but not dexamethasone is treatment of choice for patients with a symptomatic chronic subdural hematoma. Functional outcome is significantly better in surgical treated patients compared to the dexamethasone treated patients at three months. The higher complication rate after dexamethasone treatment, higher number of required additional therapy, as well as longer duration of hospital admission all contribute to a less favorable outcome. Furthermore, the delayed recovery in dexamethasone patients leads to an intensified necessary radiological monitoring. With the pressure on health care and health care costs, it is highly important to take these aspects into account. We expect treatment with dexamethasone will result in significantly increased healthcare costs. Surgery remains the best practice for symptomatic patients with a symptomatic chronic subdural hematoma.

Furthermore, a better treatment outcome in terms of recurrence risk is observed in chronic subdural hematoma without hyperdense components. Optimization of patient selection to improve treatment outcome based on symptom severity combined with radiological hematoma subtype, might contribute to improved results by tailoring treatment.

Future perspectives

Optimizing treatment

Considering the high morbidity and overall short to mid-term mortality further refinement of treatment outcome for symptomatic chronic subdural hematoma is of major importance. Several trials are currently ongoing to explore the effect of adjuvant pharmacological therapy to surgery to optimize surgical treatment effects [17,18,21,63-66]. It has been suggested that tranexamic acid is capable of hematoma volume reduction by its anti-fibrinolytic and anti-inflammatory effects [16,67-70]. To confirm the postulated beneficial effects of previous cohort studies [16,68-70], three randomized trials are ongoing to explore the effect of peri-operative tranexamic acid [63-65].

Although we have demonstrated that dexamethasone monotherapy is ineffective in symptomatic chronic subdural hematoma, there might be a beneficial effect of corticosteroids in a short-lasting peri-operative dosing scheme (or a one-time pre-operative bolus) compared to surgery without additional treatment. In the DEX-CSDH trial pre-operative dexamethasone treatment resulted in fewer repeat surgery for hematoma recurrence (1.7%) compared to the placebo group (7.1%). Hematoma with hyperdense components comprise a higher inflammatory response in the subdural space and subsequently a higher hematoma recurrence rate. On pathophysiological basis, a short peri-operative dexamethasone course could improve post-operative recovery without the complications that were observed related to prolonged corticosteroid treatment [10]. Three currently ongoing randomized trials will answer the question whether dexamethasone can be used as an adjunct to surgery to reduce hematoma recurrence and improve functional outcome [17, 18, 21].

Finally, as an extension to the spectrum of pharmacological treatment strategies, the administration of local versus general anesthesia might also influence postoperative functional outcome and complications [71-74]. Previous data from cohort studies have suggested that general anesthesia is associated with higher morbidity and mortality rates compared to local anesthesia. Therefore, future studies in a randomized manner are warranted and ongoing to explore the role of anesthesia on treatment outcome [75,76].

Data improvement

There is a significant increase in the number of chronic subdural hematoma research papers in recent years. However, the wide variation in outcome measures, study design and definitions preclude a proper assessment and comparison. Improvement of data-quality by achieving an (inter-)national consensus on the type and definition of primary outcome measures, including patient related outcome measures as well as radiological markers and measurement techniques, is of major importance. In achieving the goal of data improvement, in 2018 the Dutch Subdural Hematoma Research group (DSHR) was established as a national collaboration to facilitate chronic subdural hematoma research and the conduction of a national treatment guideline [77]. Additionally, the International Collaborative Research Initiative on Chronic Subdural Hematoma (iCORIC) study group was formed in 2019 [78]. The iCORIC aims to improve future studies on chronic subdural hematoma and facilitate the collaboration between different research groups internationally. The Defining Core Outcomes and Data Elements (CODE) in chronic subdural hematoma study, which was initiated in 2021 by the iCORIC study group, focusses on standardized outcomes that should be reported in all chronic subdural hematoma studies [79].

Prognostic radiological markers

Available studies in current literature did not assess radiological parameters in relation to functional outcome, but merely on hematoma recurrence risk. In addition to the limitation that different definitions were maintained to assess recurrence, recurrence risk does not accurately reflect the patients' functional recovery at follow up. Future radiological studies, using standardized radiological parameters and measurement techniques, are therefore warranted that focus on functional outcome, to confirm our results regarding the prognostic value of radiological hematoma subtypes on treatment outcome.

In our meta-analysis no magnetic resonance imaging (MRI) studies were included. However, MRI of chronic subdural hematoma is a very promising technique to visualize hematoma characteristics [80-84]. The correlation of inflammatory markers in the subdural fluid with specific MRI-characteristics could provide more insight into the inflammatory response in the subdural space, resulting in possible additional therapeutic options. Furthermore, this technique is much more sensitive to detect membranes and layering within a chronic subdural hematoma compared to CT scan [85-86]. Less is known whether the presence of hematoma membranes and layering are of

influence on treatment effects after surgery or dexamethasone. Identification of these structures might aid the surgeon in the surgical procedure to achieve optimal hematoma drainage. Although an MRI is more time-consuming and more expensive, future MRI studies might elucidate whether baseline MRI-evaluation contributes to a better patient selection for the purpose of personalized treatment, thus increasing the cost-effectiveness. The DECSA trial consists of an MRI – substudy in symptomatic patients with chronic subdural hematoma. Hopefully, pooled analyses of the collected MRI data with data of future prospective (observational) MRI-studies will contribute to a better understanding of imaging characteristics related to the inflammatory response in the subdural space and visualize more details on hematoma architecture and its prognostic value in functional outcome.

Prognostic clinical markers

Elucidating prognostic clinical markers are at least as important as the establishment of radiological markers for the development of a prediction model for treatment outcome. Many clinical parameters have been suggested to be of prognostic value to predict functional outcome or hematoma recurrence [46,48,52,31,33,37,87-91]. Previous studies suggested older age, male sex, and severe clinical symptoms to be associated with a worse outcome. These studies had large heterogeneity in study population and design, as well as differences in outcome measures. Future epidemiological studies using uniform definitions and outcome measures are therefore warranted to achieve more insight in prognostic clinical parameters.

The Markwalder Grading Scale does not capture the diverse neurological symptoms in patients with a chronic subdural hematoma. For example, patients with an Markwalder Grading Scale score of 2 might have seizures, but also cognitive deficits or variable severity of observed hemiparesis. It might therefore be useful to categorize patients in a refined, more extensive symptom classification system as an upgrade to the current Markwalder Grading Scale – classification. This way we might differentiate whether patients with specific symptoms do not need further treatment and which patients need urgent treatment. Patients with cognitive symptoms for example might need faster treatment. In a recently published review by the DSHR, the authors report cognitive symptoms to be present in 45% of patients which improved significantly in two-thirds after surgery [92]. Therefore, future studies are warranted to improve the existing Markwalder Grading Scale classification of symptoms [93]. Refinement of this classification system would improve our

understanding of treatment effects in specific clinical subgroups and optimize patient selection.

In summary, future studies are essential to establish clinical as well as radiological predictors to optimize patient selection and to improve treatment outcome. The use of radiological hematoma subtypes, potentially supplemented by specific MRI-characteristics, might be a promising prognostic marker for personalized medicine to achieve best treatment selection. The refinement of the symptom classification scale contributes furthermore to an improved selection of patients. Future studies are also warranted to improve surgical treatment and explore the scope of (additional) dexamethasone therapy without compromising on patient safety and efficacy. By the establishment of the DSHR as well as the iCORIC study group we aim to facilitate national and international collaboration on chronic subdural hematoma research and management.

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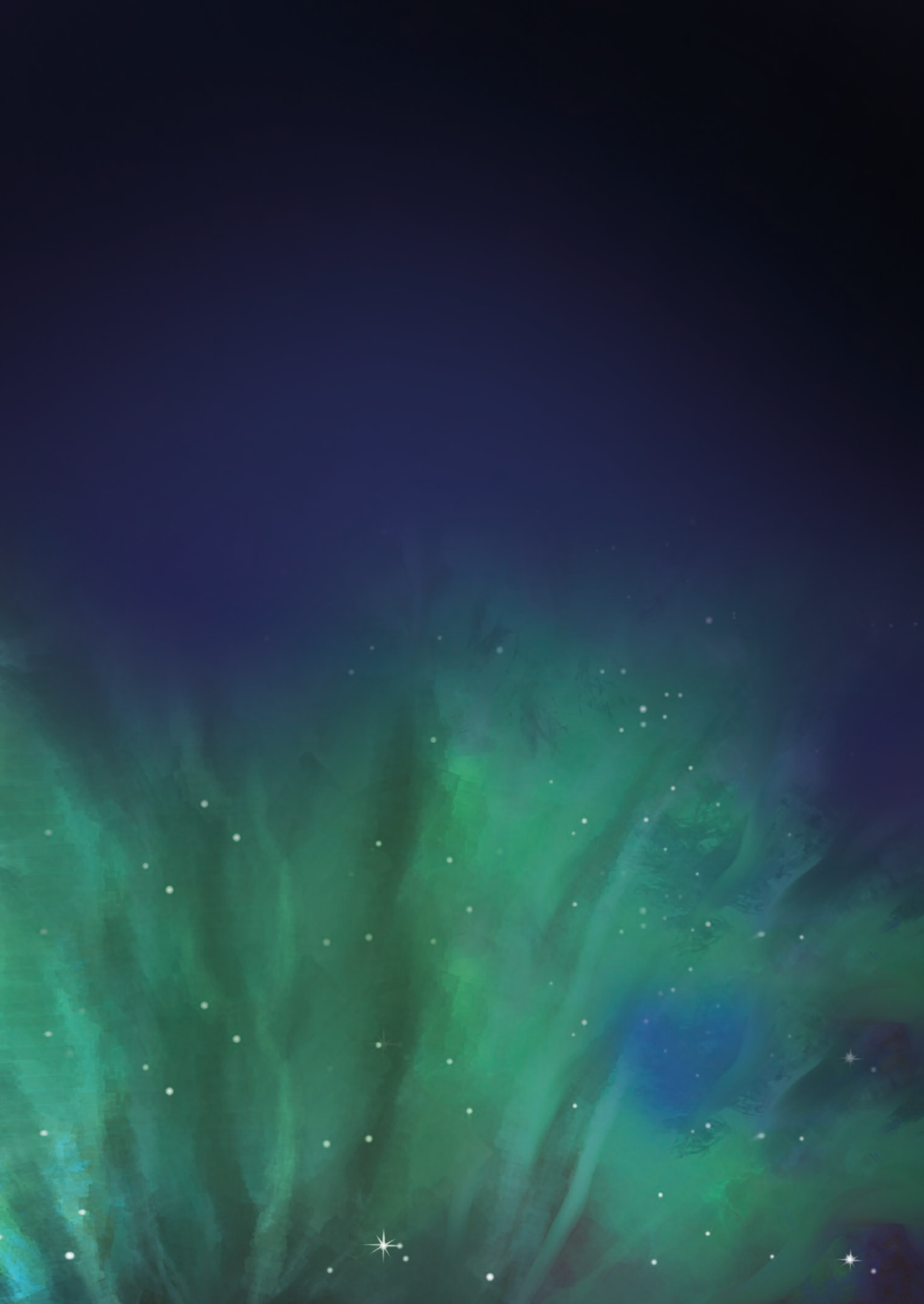


8

Supplementary appendices
Nederlandse samenvatting
Dankwoord
Curriculum vitae

Supplementary appendices

Chapter 4

Table S1. Participating Hospitals

Hospital	Number of inclusions
Admiraal de Ruyter Hospital, Goes (referring to Erasmus Medical Center)	4
Albert Schweitzer Hospital, Dordrecht (referring to Erasmus Medical Center)	12
Erasmus Medical Center, Rotterdam	2
Groningen University Medical Center, Groningen	8
Haaglanden Medical Center, The Hague	105
Haga Hospital, The Hague	38
Isala Hospital, Zwolle	12
Leiden University Medical Center	37
Maasstad Hospital, Rotterdam (referring to Erasmus Medical Center)	11
Medisch Spectrum Twente, Enschede	13
Sint Franciscus Gasthuis and Vlietland Hospital, Rotterdam (referring to Erasmus Medical Center)	6
Van Weel Bethesda Hospital, Dirksland (referring to Erasmus Medical Center)	4
Total number of inclusions	**252**

Table S2. Supplemental data on treatment

Variable	Dexamethasone	Burr-hole craniostomy
Use of antithrombotic medication during surgery– no./total no. (%)	4/71 (5.6)	12/118 (10.2)
Amount of burr holes in primary surgery– no./total no. (%)		
1 burr hole	51/71 (71.8)	89/118 (75.4)
2 burr holes	20/71 (28.2)	29/118 (24.6)
Drain placement in primary surgery– no./total no. (%)		
None	0/71 (0.0)	1/118 (0.8)
Subdural drain	55/71 (77.5)	98/118 (83.1)
Subgaleal drain	9/71 (12.7)	13/118 (11.0)
Unknown which type of drain	7/71 (9.9)	6/118 (5.1)
Type of anesthesia in primary surgery– no./total no. (%)		
Local	40/70 (57.1)	71/118 (60.2)
General	30/70 (42.9)	46/118 (39.0)
Unknown	0/70 (0.0)	1/118 (0.8)
Duration of dexamethasone tapering course – days		
Median (min-max)	19 (1-29)	n.a.
Mean ± standard deviation	15.99 ± 5.9	n.a.
IQR	14.3-19.0	n.a.
Duration between diagnosis and operation in patients randomized for dexamethasone – days		
Median (min-max)	20 (1-127)	n.a.
Mean ± standard deviation	24.31 ± 21.24	n.a.
IQR		n.a.
Duration between diagnosis and operation in patients randomized for surgery – days		
Median (min-max)	n.a.	2 (0-127)
Mean ± standard deviation	n.a.	5.16 ± 12.77
IQR	n.a.	1.0-5.0
Compliance with dexamethasone tapering course – no./total no. (%)		
Shorter dexamethasone course	43/127 (33.9)	n.a.
Full dexamethasone course	75/127 (59.1)	n.a.
Longer dexamethasone course	6/127 (4.7)	n.a.
Missing	3/127 (2.4)	n.a.

Table S2. *continued*

Variable	Dexamethasone	Burr-hole craniostomy
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)
Falling	19/127 (15.0)	9/125 (7.2)
Hyperglycaemia	25/127 (19.7)	5/125 (4.0)
Delirium	20/127 (15.7)	7/125 (5.6)
Epilepsy	16/127 (12.6)	9/125 (7.2)
Insomnia	6/127 (4.7)	4/125 (3.2)
Thrombus (total no.)	4/127 (3.1)	3/125 (2.4)
Pulmonary	3 (75.0)	1 (33.3)
Other	1 (25.0)	2 (66.7)
Mood disorder	6/127 (4.7)	0/125 (0.0)
Fever	3/127 (2.4)	1/125 (0.8)
Weight gain / increased appetite	4/127 (3.1)	0/125 (0.0)
Bleeding burr-hole pathway	2/127 (1.6)	2/125 (1.6)
Wound leakage	1/127 (0.8)	2/125 (1.6)
Gastrointestinal bleeding	1/127 (0.8)	0/125 (0.0)

Table S3. Supplemental table at three months – AS TREATED

Variable	Dexamethasone only	Dexamethasone, additional burr-hole craniostomy	Burr-hole craniostomy only	Burr-hole craniostomy, additional dexamethasone	No treatment
modified Rankin Scale score at 3 months – no./total no. (%)	N=62; 2 missing	N=65; 1 missing	N=108; 1 missing	N=12; 0 missing	N=5; 0 missing
0: No symptoms	13/60 (21.7)	8/64 (12.5)	38/107 (35.5)	3/12 (25.0)	3/5 (60.0)
1: No clinically significant disability	18/60 (30.0)	13/64 (20.3)	37/107 (34.6)	4/12 (33.3)	2/5 (40.0)
2: Slight disability	13/60 (21.7)	12/64 (18.8)	11/107 (10.3)	1/12 (8.3)	0/5 (0.0)
3: Moderate disability	6/60 (10.0)	18/64 (28.1)	11/107 (10.3)	1/12 (8.3)	0/5 (0.0)
4: Moderately severe disability	6/60 (10.0)	6/64 (9.4)	9/107 (8.4)	2/12 (16.7)	0/5 (0.0)
5: Severe disability	1/60 (1.7)	2/64 (3.1)	0/107 (0.0)	0/12 (0.0)	0/5 (0.0)
6: Dead	3/60 (5.0)	5/64 (7.8)	1/107 (0.9)	1/12 (8.3)	0/5 (0.0)

Table S4. Additional supplemental baseline data; not referred to in the manuscript

Variable	Dexamethasone	Burr-hole craniostomy
Residence prior to chronic subdural hematoma diagnosis – no./total no. (%)		
At home	118/127 (92.9)	115/125 (92.0)
Residential home	3/127 (2.4)	3/125 (2.4)
Nursing home	2/127 (1.6)	2/125 (1.6)
Rehabilitation centre	1/127 (0.8)	1/125 (0.8)
Unknown	3/127 (2.4)	4/125 (3.2)
modified Rankin Scale score at admission – no./total no. (%)		
1: No clinically significant disability	14/126 (11.1)	17/124 (13.7)
2: Slight disability	18/126 (14.3)	40/124 (32.3)
3: Moderate disability	16/126 (12.7)	23/124 (18.5)
4: Moderately severe disability	72/126 (57.1)	41/124 (33.1)
5: Severe disability	6/126 (4.8)	3/124 (2.4)
Markwalder Grading Scale at discharge – no./total no. (%)	6.25 (3.33-11.11)¶	
0: Neurologically intact	11/122 (9.0)	52/110 (47.3)
1: Alert, oriented. Mild symptoms such as headache.	57/122 (46.7)	44/110 (40.0)
2: Drowsy or disoriented with variable deficits.	48/122 (39.3)	14/110 (12.7)
3: Stuporous; responding to stimuli, severe focal signs.	1/122 (0.8)	0/110 (0.0)
4: Comatose with absent motor responses	0/122 (0.0)	0/110 (0.0)
5: Death	5/122 (4.1)	0/110 (0.0)
Markwalder Grading Scale at 2 weeks – no./total no. (%)	2.50 (1.45-4.35)¶	
0: Neurologically intact	26/115 (22.6)	49/114 (43.0)
1: Alert, oriented. Mild symptoms such as headache.	42/115 (36.5)	47/114 (41.2)
2: Drowsy or disoriented with variable deficits.	42/115 (36.5)	16/114 (14.0)
3: Stuporous; responding to stimuli, severe focal signs.	1/115 (0.9)	0/114 (0.0)
4: Comatose with absent motor responses	0/115 (0.0)	0/114 (0.0)
5: Death	4/115 (3.5)	2/114 (1.8)
Ordinal modified Rankin Scale score at discharge – no./total no. (%)	3.57 (2.00-6.25)¶	
0: No symptoms	3/114 (2.6)	22/104 (21.2)
1: No clinically significant disability	18/114 (15.8)	34/104 (32.7)
2: Slight disability	19/114 (16.7)	20/104 (19.2)
3: Moderate disability	34/114 (29.8)	15/104 (14.4)
4: Moderately severe disability	35/114 (30.7)	13/104 (12.5)
5: Severe disability	0/114 (0.0)	0/104 (0.0)
6: Dead	5/114 (4.4)	0/104 (0.0)
Ordinal modified Rankin Scale score at two weeks – no./total no. (%)	2.50 (1.47-4.35)¶	
0: No symptoms	14/111 (12.6)	31/110 (28.2)
1: No clinically significant disability	19/111 (17.1)	31/110 (28.2)
2: Slight disability	19/111 (17.1)	24/110 (21.8)
3: Moderate disability	26/111 (23.4)	9/110 (8.2)
4: Moderately severe disability	23/111 (20.7)	11/110 (10.0)
5: Severe disability	6/111 (5.4)	2/110 (1.8)
6: Dead	4/111 (3.6)	2/110 (1.8)

Table S4. *continued*

Variable	Dexamethasone	Burr-hole craniostomy
Other presenting symptoms – no./total no. (%)		
Reflex abnormalities	16/127 (12.6)	4/125 (3.2)
Ataxia	11/127 (8.7)	11/125 (8.8)
Neglect/extinction	16/127 (12.6)	11/125 (8.8)
Apraxia	5/127 (3.9)	6/125 (4.8)
Hemianopsia	5/127 (3.9)	1/125 (0.8)
Decreased consciousness	4/127 (3.1)	4/125 (3.2)
Cranial nerve deficit	10/127 (7.9)	2/125 (1.6)
Diplopia	1/127 (0.8)	1/125 (0.8)
Sensible loss	4/127 (3.1)	8/125 (6.4)
Vertigo	4/127 (3.1)	6/125 (4.8)
Syncope	1/127 (0.8)	4/125 (3.2)
Incontinence	7/127 (5.5)	4/125 (3.2)
Duration between trauma and diagnosis – days		
Median (min-max)	42 (0-122)	42 (0-147)
Mean ± standard deviation	42.49 ± 26.26	45.61 ± 34.63
Other coexisting medical conditions – no./total no. (%)		
Heart valve disease	11/127 (8.7)	7/125 (5.6)
Deep venous thrombosis / Pulmonary embolism	8/127 (6.3)	7/125 (5.6)
Dementia	7/127 (5.5)	2/125 (1.6)
Chronic Obstructive Pulmonary Disease	7/127 (5.5)	11/125 (8.8)
Liver disease	2/127 (1.6)	2/125 (1.6)
Malignancy (current and/or in the past)	25/127 (19.7%)	16/125 (12.8)
Hypertension	58/127 (45.7)	59/125 (47.2)
Congestive heart failure	10/127 (7.9)	9/125 (7.2)
Hypercholesterolemia	17/127 (13.4)	16/125 (12.8)
Kidney disease	11/127 (8.7)	6/125 (4.8)
Epilepsy	4/127 (3.1)	0/125 (0.0)
Chronic subdural hematoma	3/127 (2.4)	1/125 (0.8)
Depression	5/127 (3.9)	2/125 (1.6)
Migraine	2/127 (1.6)	3/125 (2.4)
Hypothyroidism	7/127 (5.5)	3/125 (2.4)
Other medical history	88/127 (69.3)	75/125 (60.0)
Unilateral or bilateral chronic subdural hematoma – no./total no. (%)		
Unilateral left	42/127 (33.1)	41/125 (32.8)
Unilateral right	42/127 (33.1)	51/125 (40.8)
Bilateral	43/127 (33.9)	33/125 (26.4)
Hematoma type – no./total no. (%)		
Homogeneous	69/127 (54.3)	47/125 (37.6)
Laminar	12/127 (9.4)	15/125 (12.0)
Separated	20/127 (15.7)	24/125 (19.2)
Trabecular	45/127 (35.4)	42/125 (33.6)
Mixed	4/127 (3.1)	12/125 (9.6)

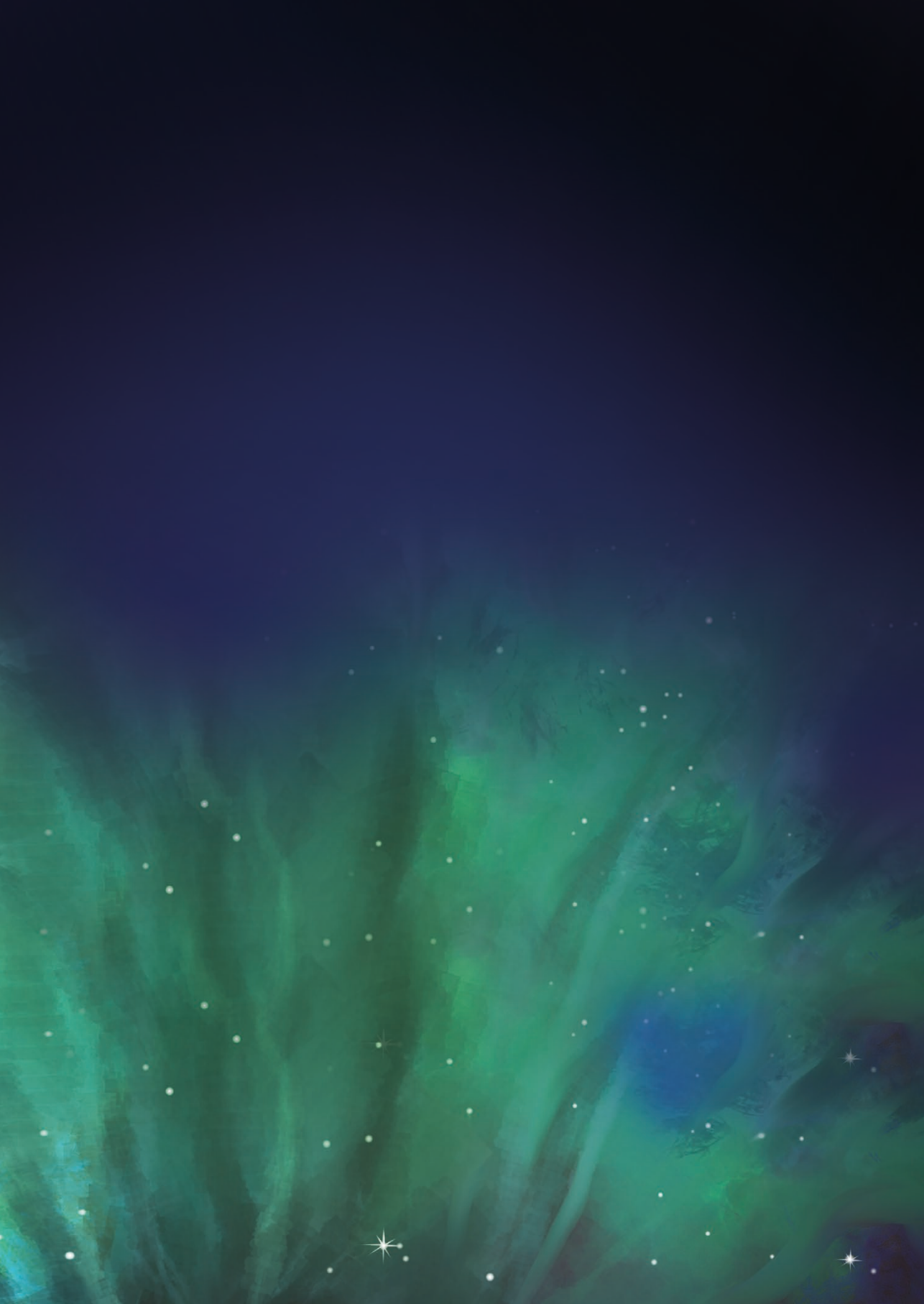
Table S4. *continued*

Variable	Dexamethasone	Burr-hole craniostomy
Type of antithrombotic medication – no./total no. (%)		
Aspirin	28/127 (22.0)	23/125 (18.4)
Clopidogrel	12/127 (9.4)	11/125 (8.8)
Vitamin K antagonists	30/127 (23.6)	25/125 (20.0)
Directly acting oral anticoagulant (DOAC)	9/127 (7.1)	8/125 (6.4)
Heparin	0/127 (0.0)	1/125 (0.8)
Other	3/127 (2.4)	2/125 (1.6)
HbA1c at diagnosis	N=92	N=83
Median (min-max)	41 (9.4-118)	39 (8-91)
Mean ± standard deviation	47.6 ± 19.4	42.1 ± 11.7

¶: Adjusted* common odds ratio

Table S5. Discharge supplementary material; not referred to in the manuscript

Variable	Dexamethasone	Burr-hole craniostomy
Discharge destination – no./total no. (%)		
Home	62/126 (49.2)	89/125 (71.2)
Residential home	3/126 (2.4)	9/125 (7.2)
Nursing home	9/126 (7.1)	8/125 (6.4)
Rehabilitation centre	34/126 (27.0)	9/125 (7.2)
Hospital	13/126 (10.3)	8/125 (6.4)
Deceased	4/126 (3.2)	0/125 (0.0)
Unknown	1/126 (0.8)	2/125 (1.6)
Glasgow Coma Scale score at discharge – no./total no. (%)		
13-15	121/122 (99.2)	120/121 (99.2)
9-12	1/122 (0.8)	1/123 (0.8)

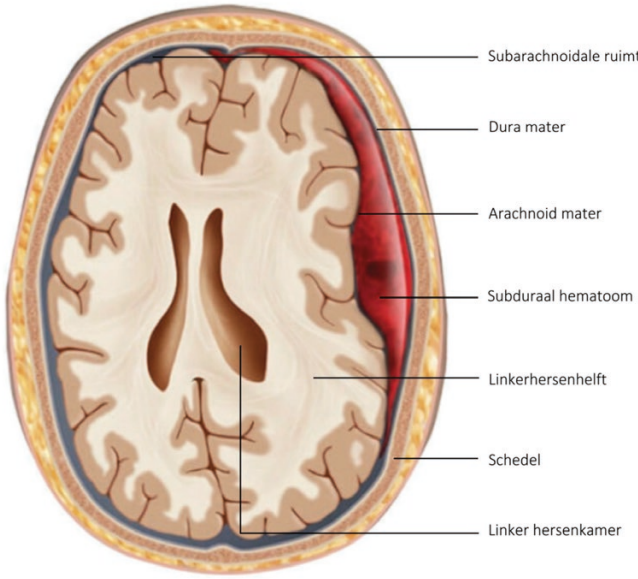


Nederlandse samenvatting

Delen uit deze Nederlandse samenvatting zijn afkomstig uit de publicatie 'Miah IP, Jellema K, Peul WC, Holl DC, Blaauw J, Van der Gaag NA. Het chronisch subduraal hematoom: uiteenlopend klinisch beeld vraagt om behandeling op maat. Nederlands Tijdschrift voor Geneeskunde 2021.' Deze Nederlandse samenvatting geeft een overzicht van de ziekte chronisch subduraal hematoom en bespreekt de onderzoeken die in dit proefschrift aan bod komen. Het proefschrift is opgedeeld in twee delen. Het eerste deel gaat over onderzoeken naar de optimale behandeling van het chronisch subdurale hematoom. Het tweede deel van het proefschrift richt zich op radiologische markers die een voorspellende waarde hebben voor het effect van de behandeling.

Ontstaansmechanisme

Het chronisch subduraal hematoom is een bloeding binnen de schedel tussen de twee buitenste hersenvliezen, de arachnoïdea en de dura mater (figuur 1). De ruimte waarin dit type bloeding zich bevindt wordt ook wel de subdurale ruimte genoemd. Afhankelijk van hoe lang dit type bloeding zich bevindt in de subdurale ruimte, wordt er onderscheid gemaakt tussen een acuut (binnen een paar dagen), subacuut (dagen tot weken) of chronisch (paar weken of langer) subduraal hematoom.



Figuur 1. Chronisch subduraal hematoom

Vaak wordt het chronisch subduraal hematoom voorafgegaan door een (gering) hoofdtrauma. Daardoor werd het voorheen beschouwd als een traumatische bloeding die ontstond door het scheuren van de afvoerende, oftewel veneuze, bloedvaten vanuit de hersenen. De gedachte was dat het chronisch subduraal hematoom zich ontwikkelde vanuit een acuut subduraal hematoom. Maar niet elk acuut subduraal hematoom wordt chronisch en niet na elk hoofdtrauma ontstaat direct een bloeding, maar ontwikkelt deze zich pas weken later. Er moet dus meer aan de hand zijn. Tegenwoordig is bekend dat het overgrote deel van deze chronische subdurale hematomen zeer waarschijnlijk ontstaat als gevolg van een ontstekingsreactie van de grenscellen van de hersenvliezen: een dunne laag cellen tussen binnenste laag van de dura mater en arachnoïdea. Deze ontstekingsreactie kan ontstaan door een trauma, infectie of een andere niet nader gedefinieerde aanleiding, waardoor er hersenvocht vrij komt in de subdurale ruimte. Dit leidt tot een opeenvolgende reactie van ontstekingscellen in de subdurale ruimte en de vorming van nieuwe, kwetsbare structuren: eiwitmembranen en kleine bloedvaten. Doordat deze structuren gemakkelijk scheuren en ter plaatse het bloedafbraakproces verhoogd is, kunnen bloedingen ontstaan in de subdurale ruimte en kan het chronisch subdurale hematoom in omvang toenemen.

Epidemiologie

Het chronisch subduraal hematoom is een veelvoorkomende neurologische aandoening met een incidentie van 5-58/100.000 inwoners. Deze aandoening komt vooral voor bij oudere patiënten met een gemiddelde leeftijd van 70-75 jaar. Naar verwachting zal het chronisch subduraal hematoom rond het jaar 2030 de meest voorkomende reden voor een neurochirurgische operatie aan de schedel zijn als gevolg van de vergrijzing van de bevolking en toename in gebruik van bloedverdunners. De belangrijkste risicofactoren voor een chronisch subduraal hematoom zijn een hoge leeftijd, afname van hersenvolume een doorgemaakt hoofdtrauma en het gebruik van bloedverdunners (antitrombotische medicatie).

Symptomen

De symptomen van de patiënt met een chronisch subduraal hematoom worden met name veroorzaakt door druk van de bloeding op het gezonde hersenweefsel. Het klachtenpatroon is uiterst variabel. Wanneer de bloeding geen druk uitoefent op het hersenweefsel kan de patiënt klachtenvrij zijn (asymptomatisch). Bij symptomatische patiënten variëren de klachten van alleen hoofdpijn, subtiele cognitieve klachten of voorbijgaande klachten, zoals een epileptische aanval, tot meer invaliderende uitval, zoals een halfzijdige

verlamming of bewustzijnsdaling. Deze klachten kunnen ontstaan en verergeren in een relatief kort tijdsbestek – dagen tot enkele weken – of juist een heel sluimerend beloop hebben. De Markwalder Grading Schaal (MGS) score is een classificatiesysteem dat met name in de onderzoekswereld gebruikt wordt om de ernst van de symptomen uit te drukken (tabel 1). Zo wordt deze score ook toegepast in de onderzoeken van dit proefschrift als meetinstrument voor patiëntselectie en het herstel van klachten.

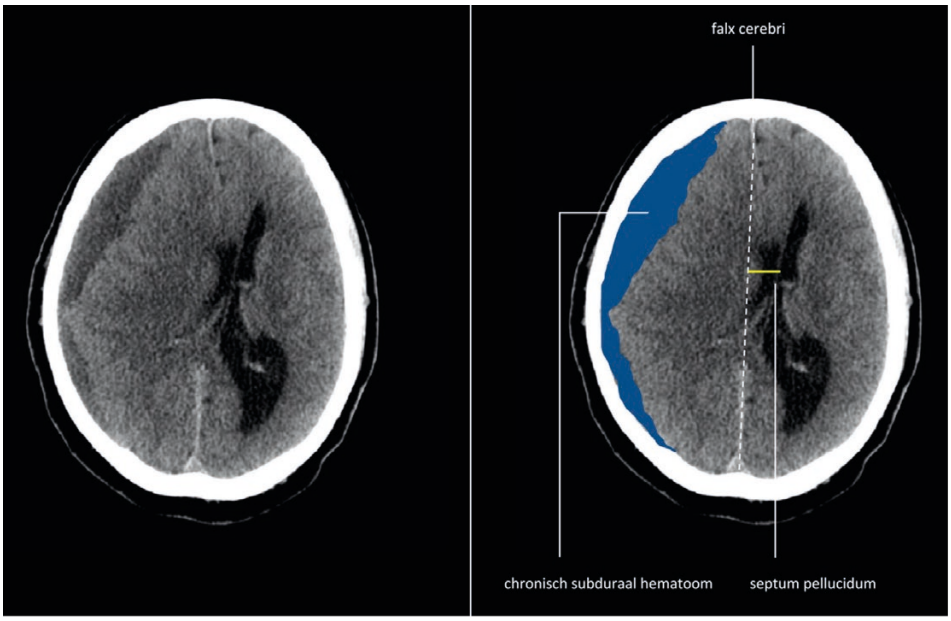
Diagnose

Over het algemeen wordt de diagnose gesteld met behulp van een computer tomografie (CT) scan omdat deze techniek snel, toereikend en kosteneffectief is. Door middel van röntgenstralen wordt er een afbeelding van de hersenen verkregen en zo ook van dit type hersenbloeding (figuur 2). De vorm van het chronisch subduraal hematoom is karakteristiek en halvemaanvormig, echter het aspect van de bloeding kan variëren afhankelijk van o.a. hoe oud de bloeding is, de aanwezigheid van verse bloedingscomponenten en schotten of compartimenten in het hematoom. In de literatuur wordt op basis van CT-kenmerken het chronisch subduraal hematoom vaak ingedeeld in vier architectuur subtypen van Nakaguchi (figuur 3, typen A-D).

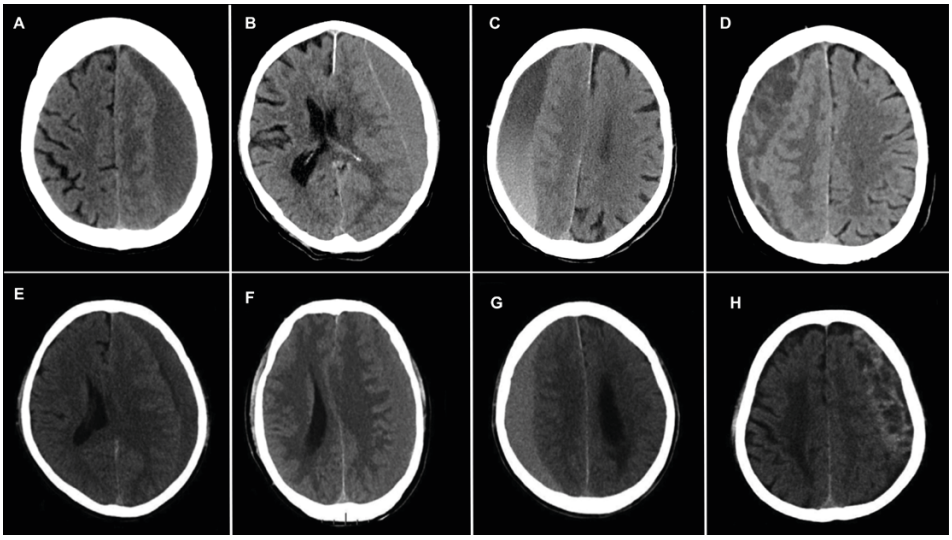
Tabel 1. Markwalder Grading Schaal

Score	Neurologische symptomen
0	Geen neurologische symptomen
1	Geringe symptomen: patiënt alert en georiënteerd, geringe symptomen zoals hoofdpijn of een reflex asymmetrie
2	Matig-ernstige symptomen: Patiënt somnolent of gedesoriënteerd (Glasgow Coma Schaal score* 13-14) met variabele neurologische uitval, zoals halfzijdige verlamming
3	Ernstige symptomen: Patiënt met verlaagd bewustzijn (Glasgow Coma Schaal score* 9-12) met nog aanwezige reactie op pijnprikkel, ernstige neurologische uitval zoals een volledige verlamming
4	Patiënt comateus zonder reactie op pijnprikkels (Glasgow Coma Schaal score* 8 of lager).

* Glasgow Coma Score is een scoringssysteem variërend van minstens 3 tot maximaal 15 punten, waarmee het bewustzijn van de patiënt wordt gescoord aan de hand van de reacties van de ogen (1-3 punten), ledematen (1-6 punten) en de verbale respons (1-5 punten) op verschillende stimuli. Een hogere score weergeeft een beter bewustzijn.



Figuur 2. CT-afbeelding van chronisch subduraal hematoom. A: CT scan van chronisch subduraal hematoom; B: blauw gearceerd deel weergeeft de bloeding. Door druk op het hersenweefsel ontstaat er een verschuiving van structuren (gele lijn), oftewel midline-shift.



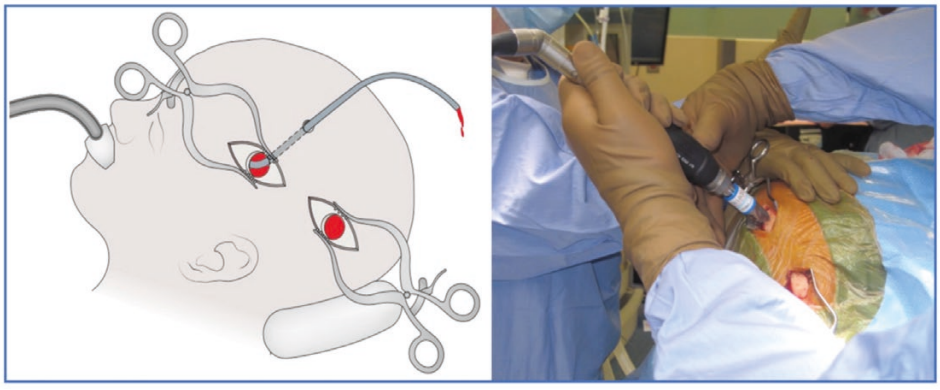
Figuur 3. Radiologische subtypen van het chronisch subduraal hematoom. Classificatie Nakaguchi (A-D): A. homogeen; B. laminair; C. gesepareerd; D. trabeculair; Radiologische subtypen o.b.v. densiteit (E-H): E. homogeen hypodens; F. homogeen isodens; G. homogeen hyperdens; H. gemengd type hematoom.

Keuze voor een behandeling

De indicatie voor behandeling wordt bepaald door de ernst van de symptomen, de radiologische kenmerken, zoals de dikte van de bloeding (schildikte), de mate van verplaatsing van het hersenweefsel (midline-shift) en de hoeveelheid acute bloedingscomponenten, en of de patiënt antitrombotische medicatie krijgt. Bij patiënten die asymptomatisch zijn of weinig klachten hebben, kan worden volstaan met een afwachtend beleid waarbij de bloeding de kans krijgt om door het lichaam zelf opgeruimd te worden. Als de patiënt echter (invaliderend) symptomatisch is, is een behandeling aangewezen om het herstel te bevorderen en verdere complicaties te voorkomen.

Operatie

Wereldwijd is een boorgatdrainage de meest toegepaste behandeling voor symptomatische patiënten. Dit betreft een operatie waarbij 1 of meerdere boorgaten in de schedel worden gemaakt om de bloeding te kunnen afvoeren (figuur 4). Deze behandeling kan onder lokale of algehele anesthesie plaatvinden. Door na de operatie gedurende 24 tot 48 uur een drain achter te laten in de subdurale ruimte, wordt het risico op een hernieuwde bloeding (recidief) meer dan gehalveerd van 21% naar 8%. Overige risico's van een operatie zijn een infectie in de subdurale ruimte (empyeem), een wondinfectie, schade aan het hersenweefsel of bloeding in het operatietraject.



Figuur 4. Boorgatdrainage

Medicatie

Gezien het risico op het herhalen van het chronisch subduraal hematoom en complicaties van een operatie bij de doorgaans oude en kwetsbare patiënten, wordt er onderzoek gedaan naar verschillende medicamenteuze therapieën. Deze therapieën hebben elk een aangrijpingspunt op de bovenbeschreven ontstekingsreactie in de subdurale ruimte. Wereldwijd is dexamethason het meest toegepaste geneesmiddel voor de behandeling van symptomatische patiënten met het chronisch subduraal hematoom. Dexamethason is een geneesmiddel met een sterk ontstekingsremmend effect en remt daarnaast ook de vorming van nieuwe bloedvaten waardoor de vermeende ontstekingsreactie en vorming van bloedvaten in de subdurale ruimte kan worden tegengegaan. De bewijskracht voor de effectiviteit van deze therapie is echter tot op heden zeer beperkt. Desondanks wordt dexamethason in verschillende Nederlandse ziekenhuizen maar ook in het buitenland regelmatig toegepast als een alternatieve behandeling of aanvullend op een operatie.

Het gebrek aan goede wetenschappelijke onderbouwing voor de toepassing van dexamethason in symptomatische patiënten met het chronisch subdurale hematoom heeft geleid tot de onderzoeken in dit proefschrift.

De optimale behandeling: medicatie of een operatie?

In het eerste deel van dit proefschrift werd onderzocht welke van de twee meest toegepaste behandelingen wereldwijd tot het beste resultaat leidt: behandeling met het geneesmiddel dexamethason of een operatie middels boorgatdrainage.

Om de effectiviteit te onderzoeken van dexamethason therapie in vergelijking tot een operatie werd als eerst de DECSA-R studie uitgevoerd (**hoofdstuk 2**): DExamethasone therapy in Chronic Subdural hematomA – a Retrospective evaluation. Dit was een retrospectief onderzoek waarbij er twee patiëntgroepen uit twee verschillende Nederlandse, neurochirurgische ziekenhuizen met elkaar werden vergeleken, elk met een eigen behandelprotocol. Patiënten met een score van MGS 1 en 2 waren geschikt voor de studie, daar in beide ziekenhuizen asymptomatische patiënten (MGS 0) niet werden behandelend en ernstig aangedane patiënten (MGS 3-4) direct werden geopereerd. Als belangrijkste uitkomstmaat van deze studie werd het herstel van de patiënt beoordeeld bij drie maanden met behulp van de Modified Rankin Scale (mRS) score: een zeven-punten schaal die de mate van zelfstandig functioneren uitdrukt variërend

van 0 (volledig zelfstandig en in staat om alle activiteiten te hervatten) tot 6 (overleden). Daarnaast werd bij drie maanden ook de symptoomernst gemeten met behulp van de MGS score. Data werd gecollecteerd door middel van dossieronderzoek.

Gedurende de onderzoeksperiode van 2014-2016 werden er 60 patiënten geïncludeerd in het eerste ziekenhuis, die allen werden geopereerd middels een boorgatdrainage met 48 uur subdurale drainage (cohort A). In dezelfde periode werden ook 60 patiënten geïncludeerd in het tweede ziekenhuis alwaar alle patiënten met dexamethason werden behandeld (cohort B). Indien de patiënt in cohort B onvoldoende verbetering toonde op dexamethason, werd aanvullend een operatie verricht middels boorgatdrainage met subdurale drain plaatsing.

Op het primaire meetmoment van drie maanden was het functioneel herstel in beide groepen statistisch niet significant verschillend. Een gunstig functioneel herstel waarbij de patiënt zelfstandig is in de Algemene Dagelijkse Levensverrichtingen (ADL), uitgedrukt in mRS score 0-3, werd bereikt in 70% van de operatiegroep (cohort A) en 76% van de dexamethason groep (cohort B). Een verbetering in symptoomernst, uitgedrukt in MGS score 0-1, werd gezien in 96% van beide groepen. In de dexamethason groep was echter in 83% een aanvullende operatie noodzakelijk om het herstel te bevorderen. Daarnaast waren de complicaties aanzienlijk hoger in de dexamethason groep in vergelijking tot de operatiegroep (55% versus 35%) en was in deze groep ook de opnameduur significant langer (10 versus 5 dagen). In beide groepen was de mortaliteit 10%.

Concluderend leidde dexamethason therapie tot de noodzaak van een aanvullende operatie in een zeer hoog percentage. Het hoge complicatie-risico als ook de lange opnameduur na dexamethason therapie zorgde ervoor dat deze behandeling niet geschikt was in de symptomatische patiënt met een chronisch subduraal hematoom.

Om deze resultaten van de DECSA-R studie te toetsen, werd de gerandomiseerde DECSA-studie opgezet: DExamethasone therapy in symptomatic patients with Chronic Subdural hematomA. Dit was een prospectief, landelijk, multicenter onderzoek waarbij symptomatische patiënten met het chronisch subduraal hematoom geloot (gerandomiseerd) werden voor dexamethason therapie of een operatie. In **hoofdstuk 3** werd het studieprotocol beschreven. De primaire uitkomstmaat van de DECSA-studie was de effectiviteit van dexamethason

therapie vergeleken met een operatie op functioneel herstel (uitgedrukt in de mRS score). Belangrijke secundaire uitkomstmaten waren de noodzaak tot een aanvullende behandeling, complicaties, opnameduur en mortaliteit. Patiënten met een symptoomernst van MGS 1-3 waren geschikt voor dit onderzoek. Patiënten die gerandomiseerd waren voor dexamethason therapie werden 19 dagen behandeld met dexamethason waarbij zij gedurende de eerste vier dagen 16 mg dexamethason innamen, waarna de dagdosering elke drie dagen werd gehalveerd tot aan staken van de therapie op dag 20. Om de kwaliteit en veiligheid van de studie te waarborgen werd een externe commissie samengesteld (Data Safety Monitoring Board, DSMB) die bij de eerste 150 en 300 patiënten bijeen zou komen om de studie te monitoren. Om te onderzoeken of dexamethason even effectief was als een operatie (non-inferieur) waren 420 patiënten in totaal nodig voor de studie, van wie 210 dexamethason zouden ontvangen en 210 een operatie.

De resultaten van de DECSA-studie werden besproken in **hoofdstuk 4**. Van september 2016 tot en met februari 2021 werden in totaal 252 patiënten geïncludeerd in de DECSA-studie afkomstig uit twaalf Nederlandse ziekenhuizen. De studie werd na de eerste bijeenkomst van de DSMB in februari 2021 voortijdig gestopt vanwege veiligheidsoverwegingen en resultaten in de dexamethason-arm. In totaal werden 127 patiënten gerandomiseerd voor dexamethason therapie en 125 patiënten voor een operatie.

Bij de evaluatie op drie maanden behaalde een significant lager percentage patiënten in de dexamethason groep een gunstig functioneel herstel - gedefinieerd als mRS score 0-2, de primaire uitkomstmaat - vergeleken met de operatiegroep, namelijk 82% versus 89%. Tevens werden er meer complicaties waargenomen in de dexamethason groep (67% versus 33%). Het risico op een infectie was 23% in de dexamethason groep en 19% in de operatiegroep, verhoogde bloedsuikers 20% en 4% en een acute verwardheidstoestand (delirium) 16% en 6% respectievelijk. De totale opnameduur was in de dexamethason groep met 12 dagen significant hoger dan de operatiegroep waarbij deze 7 dagen was. Tot slot was de mortaliteit ook hoger in de dexamethason groep (6% versus 2%), alhoewel dit verschil niet significant bleek. Uiteindelijk had 61% van de dexamethason groep een aanvullende behandeling nodig waarbij dit in 56% bestond uit een aanvullende operatie en 5% een tweede dexamethason kuur. Een aanvullende operatie werd verricht na een mediane behandelduur van 20 dagen. In de operatiegroep was het percentage patiënten dat een aanvullende therapie nodig had significant lager,

namelijk 17%. Van hen ontving 10% aanvullend dexamethason therapie en een tweede operatie (re-operatie) in 6%.

Gebaseerd op deze resultaten van de DECSA-studie, werd geconcludeerd dat dexamethason therapie tot een slechter functioneel herstel heeft geleid vergeleken met een operatie in symptomatische patiënten met het chronisch subduraal hematoom. Een aanvullende operatie leek alsnog nodig in de meerderheid van de patiënten, met daarnaast een hoger complicatie-risico en een langere opnameduur.

Voorspellende factoren voor de uitkomst van een behandeling

Het chronisch subduraal hematoom kan per patiënt er anders uitzien op een CT-scan. Zoals bovenbeschreven zijn er verschillende radiologische hematoom typen te identificeren (figuur 3). Ook de grootte van de bloeding, uitgedrukt in schildikte, midline-shift (mate van verschuiving hersenstructuren, figuur 2) en hematoom volume en de locatie van de bloeding, een- of tweezijdig aanwezig (uni- of bilateraal respectievelijk), zijn belangrijke radiologische variabelen. Interessant is daarom om te weten of er radiologische kenmerken zijn die ten tijde van de diagnosestelling het behandeleffect kunnen voorspellen.

Om dit te onderzoeken, werd in het tweede deel van dit proefschrift eerst een systematisch literatuuronderzoek (review en meta-analyse) verricht **(hoofdstuk 5)**. Hiervoor werden elektronische medische databases doorzocht vanaf de periode 1940 tot en met 2020 naar studies in chronisch subduraal hematoom patiënten die operatief werden behandeld. Radiologische parameters die voor dit onderzoek beoordeeld werden op hun voorspellende waarde voor het behandeleffect, waren: hematoomzijde (uni- of bilateraal), schildikte in millimeters (mm), midline-shift in mm en tot slot de acht radiologische hematoom subtypen op basis van architectuur en densiteit (figuur 3: A-H). Het behandeleffect werd uitgedrukt in het risico op een hernieuwd (recidief) chronisch subduraal hematoom na een eerste operatie. Er werden in totaal 3112 wetenschappelijke publicaties gevonden. Honderd hiervan toonden resultaten van CT-scan karakteristieken. In totaal voldeden 22 studies aan de gedefinieerde kwaliteitseisen en konden deze studies geïncludeerd worden voor de systematische review en meta-analyse. Deze studies vormden in totaal

een patiëntpopulatie van 5566 patiënten met een gemiddelde leeftijd van 70 jaar. Een hernieuwd chronisch subduraal hematoom trad op in 14%.

Een analyse van de onderzochte radiologische parameters liet zien dat de classificatie van radiologische hematoom subtypen de grootste voorspellende waarde heeft van het behandeleffect. Chronisch subdurale hematomen met recente (actieve) bloedingscomponenten toonden het hoogste recidief risico. Ook het formaat van de bloeding had een voorspellende waarde. Bloedingen die groter waren dan de tevoren gedefinieerde afkapwaarden door de onderzoekers in de verschillende studies, toonden ook een hoger herhaal risico maar het voorspellende effect van deze afmetingen was kleiner dan het effect van de radiologische hematoom subtypen.

Geconcludeerd werd dat het behandeleffect van een operatie het slechtst was in chronisch subdurale hematomen waarin recente (actieve) bloedingscomponenten aanwezig waren. De identificatie van deze risicogroep is van belang voor het optimaliseren van de therapie. Een geïndividualiseerde behandeling kan mogelijk bijdragen aan betere behandelresultaten.

In de DECSA-studie werd bewezen dat een operatie de geschikte behandeling is voor symptomatische patiënten met een chronisch subduraal hematoom. Een kleine subgroep echter, toonde verbetering onder dexamethason therapie. In 39% van de studiepatiënten die met dexamethason werden behandeld, werd namelijk geen aanvullende operatie verricht. De systematische review had aangetoond dat het radiologisch hematoom subtype het behandeleffect van een operatie kon beïnvloeden. Mogelijk verschilt ook het effect van dexamethason therapie in de verschillende radiologische hematoom subtypen, daar de verscheidene subtypen verschillende stadia van het hematoom (en mogelijk ook van de vermeende ontstekingsreactie in de subdurale ruimte) weerspiegelen. Om te onderzoeken in welk radiologisch hematoom subtype het effect van dexamethason het grootst was, werd in **hoofdstuk 6** een CT-studie uitgevoerd in de patiënten die met dexamethason waren behandeld. Het doel van dit onderzoek was om vast te stellen in welk radiologisch subtype (figuur 3, tabel 2) het effect van dexamethason zowel radiologisch als klinisch het grootst was. Dit effect werd gemeten aan de hand van de afname van het chronisch subdurale hematoom op de controle CT-scan na 14 dagen behandeling, maar ook het klinisch herstel van de patiënt. Dit onderzoek vormde een onderdeel (substudie) van het DECSA-onderzoek en werd uitgevoerd in drie neurochirurgische centra. Patiënten die voor dexamethason werden gerandomiseerd in de deelnemende

ziekenhuizen waren geschikt voor deze studie. Dexamethason werd conform het behandelschema uit de DECSA-studie toegepast.

In totaal werden van 2016 tot 2021 85 patiënten geïncludeerd in dit CT-onderzoek die allen met dexamethason werden behandeld. De resultaten toonden dat chronisch subdurale hematomen zonder recente (actieve) bloedingscomponenten (figuur 3, subtype E en F) een significant grotere afname radiologisch van de bloeding lieten zien na 14 dagen behandeling vergeleken met hematomen met recente (actieve) bloedingscomponenten (figuur 3, subtype G en H). Zowel de afname van de schildikte als ook de druk op het hersenweefsel door de bloeding met als gevolg verplaatsing van de hersenstructuren (midline-shift) was het grootst in deze groep zonder recente (actieve) bloedingscomponenten. Ook het percentage patiënten die klinisch verbetering toonde onder dexamethason therapie was het hoogst in patiënten waarin ook de radiologische afname het grootst was (subtype E en F). In 54% van de patiënten was een aanvullende operatie nodig, met het hoogste risico in de groep patiënten met hematomen van het gesepareerde subtype (figuur 3, type C).

Dit onderzoek toonde aan dat dexamethason therapie radiologisch het grootste effect bereikte in hematomen zonder recente (actieve) bloedingscomponenten. Het risico op een aanvullende operatie was daarnaast het hoogst in patiënten met een gesepareerd hematoom subtype. Door een verbeterde patiëntselectie kan mogelijk het effect van dexamethason therapie worden vergroot.

De conclusies van dit proefschrift

De onderzoeken van dit proefschrift hebben aangetoond dat een operatie tot een beter behandelresultaat leidt in symptomatische patiënten met het chronisch subduraal hematoom dan behandeling met dexamethason therapie. De meerderheid van de patiënten die met dexamethason werd behandeld, had alsnog een operatie nodig. Dexamethason therapie gaf een hoger risico op complicaties en een langere ziekenhuisopnameduur in vergelijking met een operatie.

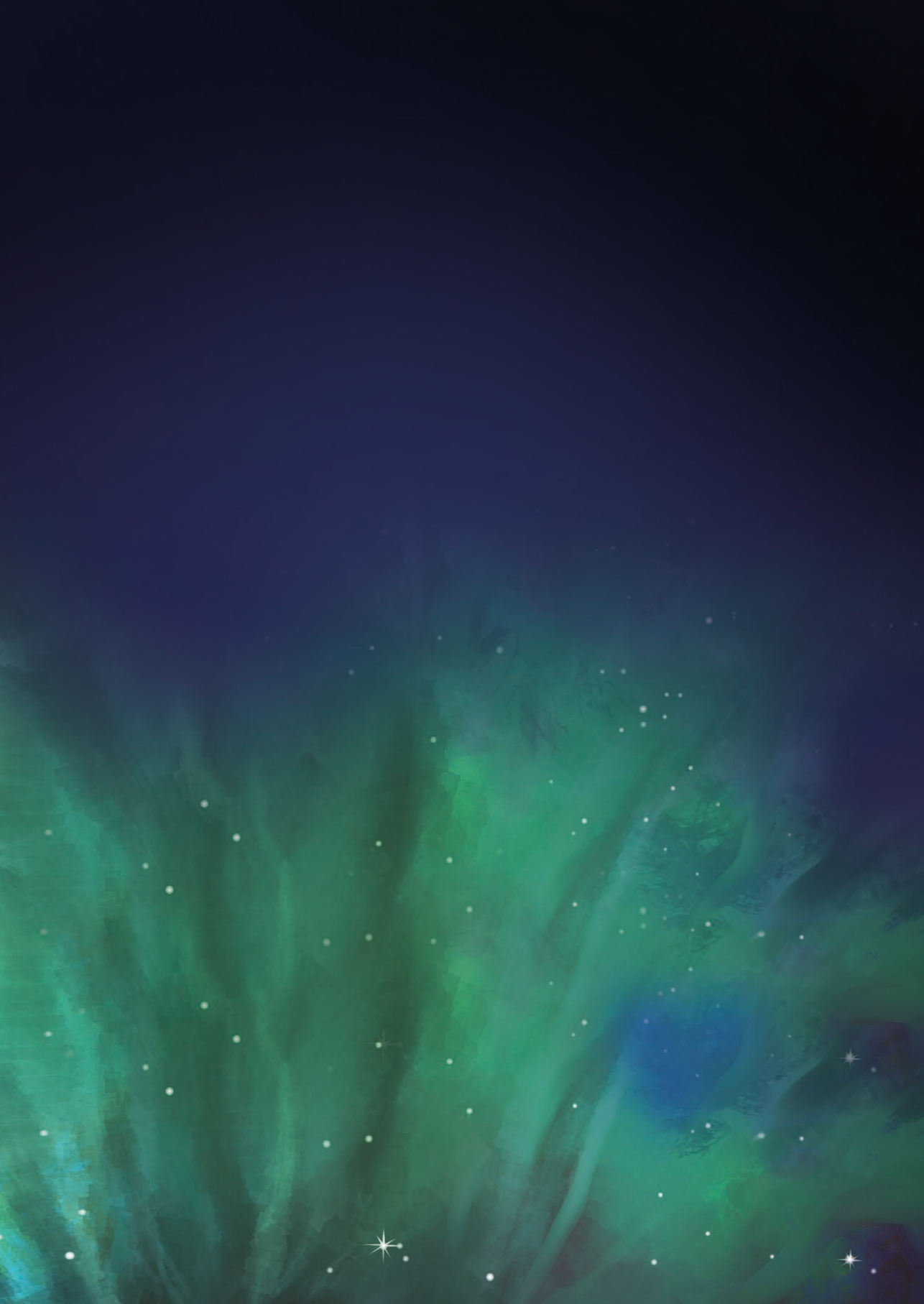
CT-kenmerken van het chronisch subduraal hematoom kunnen het behandeleffect voorspellen. Het resultaat van een operatie was slechter in hematomen met recente (actieve) bloedingscomponenten vergeleken met

hematomen zonder deze recente (actieve) bloedingscomponenten. Ook het effect van dexamethason was slechter in dit radiologische subtype. Het grootste behandeleffect (radiologisch en klinisch) na dexamethason therapie werd waargenomen in chronisch subdurale hematomen zonder recente (actieve) bloedingscomponenten.

Toekomstig onderzoek

De identificatie van risicogroepen is van belang om de behandeling van patiënten met het chronisch subdurale hematoom te optimaliseren. Niet alleen radiologische kenmerken voorspellen het behandeleffect, maar ook klinische parameters zoals leeftijd, geslacht en type en ernst van de symptomen. Dit opent deuren voor toekomstig onderzoek. Specifieke technieken voor beeldvormende diagnostiek zoals Magnetic Resonance Imaging (MRI) – kenmerken, kunnen bijdragen aan de identificatie van voorspellende radiologische markers. Een verfijning van de huidige symptoomernst classificatie-schaal, de MGS-score welke uit slechts vijf grove categorieën bestaat, zal ook leiden tot een betere patiëntselectie. Toekomstig onderzoek is daarnaast nodig om operatieve technieken te optimaliseren. Tot slot zullen door de resultaten van de DECSA-studie onderzoeken met dexamethason schaars worden in de toekomst. Daarom is het van belang om juist in dit stadium te evalueren of er nog ruimte is voor dexamethason therapie in een select patiëntengroep om veilig en effectief toegepast te kunnen worden.

Om onderzoek in grote patiëntengroepen met een specifiek radiologisch en klinisch chronisch subduraal hematoom subtype mogelijk maken, is samenwerking landelijk en internationaal van groot belang. Hiertoe werd de landelijke werkgroep ‘Dutch Subdural Hematoma Research Group’ (DSHR) en de internationale werkgroep ‘International COllaborative Research Initiative on Chronic Subdural Hematoma’ (ICORIC) opgericht. Door gezamenlijke doelen, heldere en eenduidige definities te formuleren, kunnen data gebundeld worden wat tot waardevolle informatie zal leiden.



Dankwoord

Dit proefschrift was niet tot stand gekomen zonder de hulp van een grote groep mensen.

Mijn dank gaat allereerst uit naar de patiënten die het vertrouwen hebben gehad in onze onderzoeksgroep. Zonder hun bijdrage hadden wij deze resultaten niet kunnen behalen.

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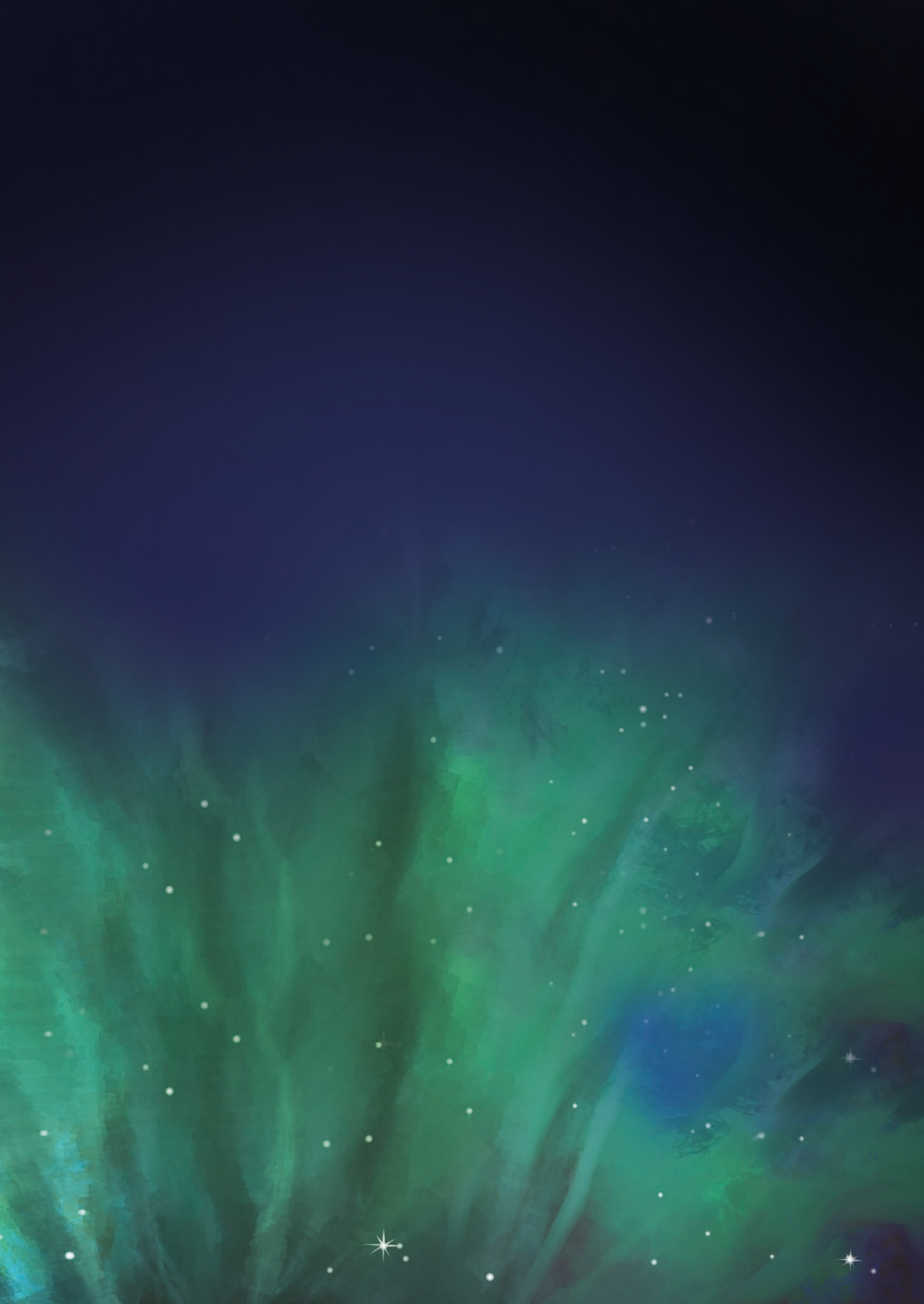

Curriculum vitae

Ishita Parveen Miah was born on February 18th in 1987 in Leiderdorp, The Netherlands. She grew up in Leiderdorp and completed high school at Het Stedelijk Gymnasium in Leiden in 2005. During her medical school at the Vrije Universiteit (VU University) Medical Center in Amsterdam she developed her interest in scientific research and neurology during her internship neurosciences. This affection developed further during her scientific internship at the department of neurology of the VU University Medical Center evaluating cognitive performance in Parkinson's disease under supervision of dr. Jan Berend Deijen and prof. dr. Henk W. Berendse. After graduating medical school in August 2011, she extended her scientific internship with a year in order to obtain her first scientific publication and combined this trajectory with her job as neurology resident at the Spaarne Hospital in Hoofddorp in October 2011.

In September 2012, Ishita continued her residency in neurology at the Haaglanden Medical Center (HMC) in The Hague to start off her Neurology Residency Program in January 2013. She soon developed an affinity with neurovascular disease and it was during the third year of her residency that she was offered the opportunity to initiate a research line in the treatment of chronic subdural hematoma. This marked the start of her PhD – trajectory at the Leiden University Medical Center under supervision of neurosurgeon prof. dr. Wilco C. Peul as her primary thesis advisor and neurologist dr. Korne Jellema and neurosurgeon dr. Niels A. van der Gaag, both as thesis co-advisors. During her residency program she developed the trial protocol for the DECSA-study in 2016 and obtained approval in the same year from the Medical Ethical Committee to initiate the trial as national study coordinator. She was able to combine the final years of her residency with scientific research by the achieved research grant from the Sint Jacobus Foundation and a scientific scholarship from the HMC-research bureau Landsteiner Institute.

After the completion of her residency program in December 2018, Ishita initiated her work as neurologist at the Leiden University Medical Center as a fellow in Vascular Neurology under mentorship of prof. dr. Marieke J. H. Wermer. In the following two years she combined clinical work with her PhD-program and finalized the studies of her thesis. In January 2021 she continued her career as neurologist with focus on vascular neurology at the Amphia Hospital in Breda.