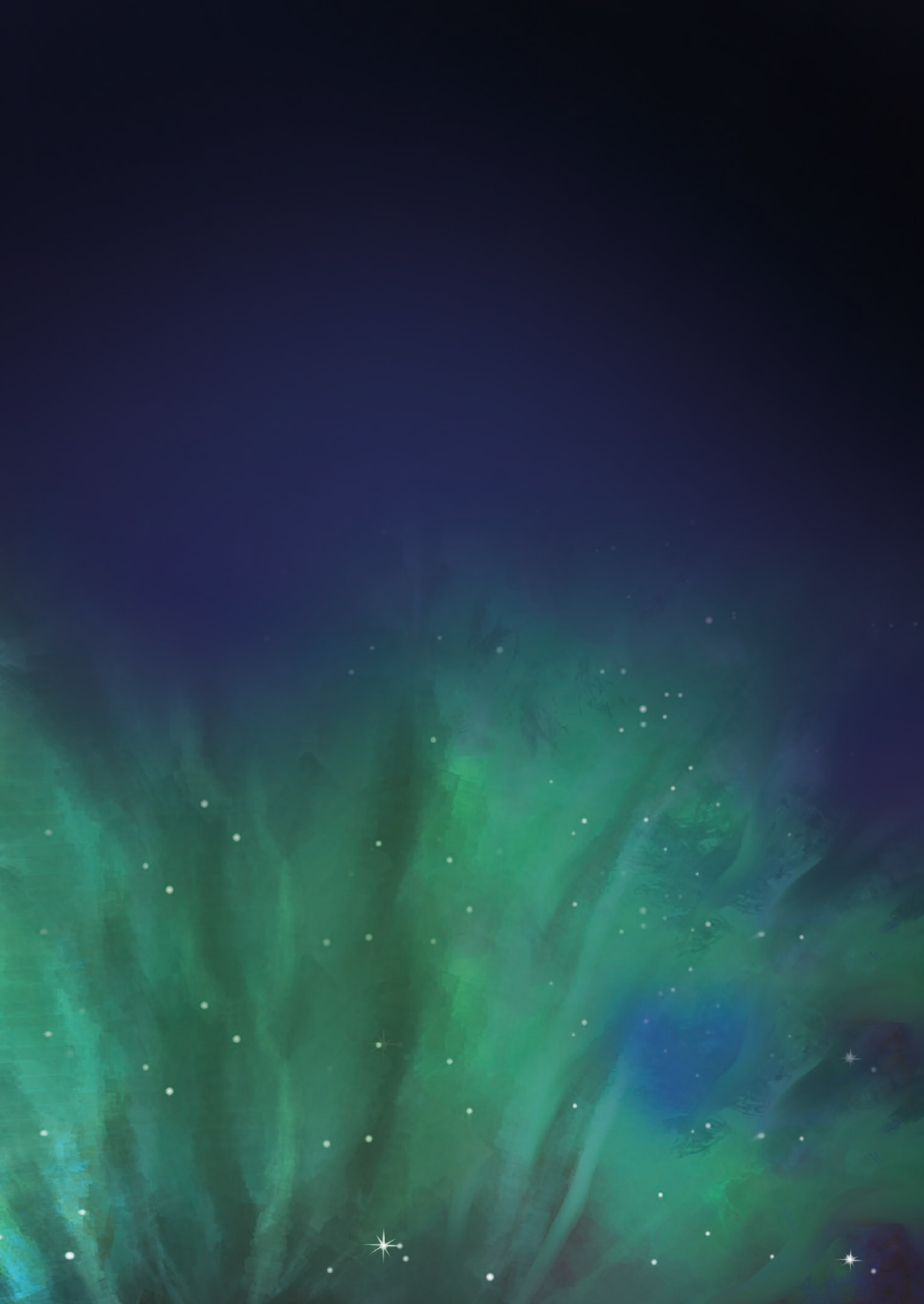
Chronic subdural hematoma: tailoring treatment

Miah, I.P.



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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].

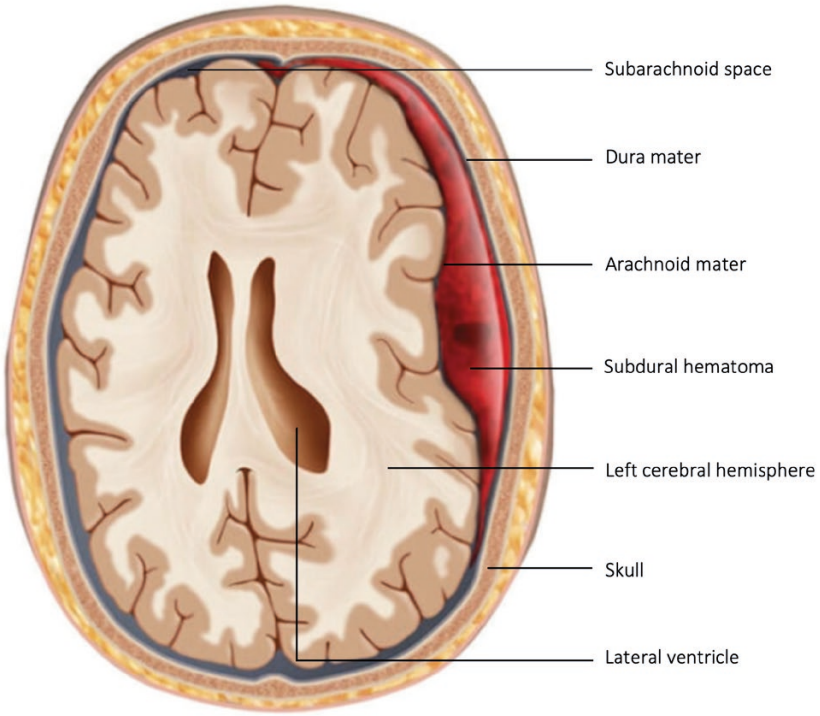

Figure 1. Chronic subdural hematoma

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

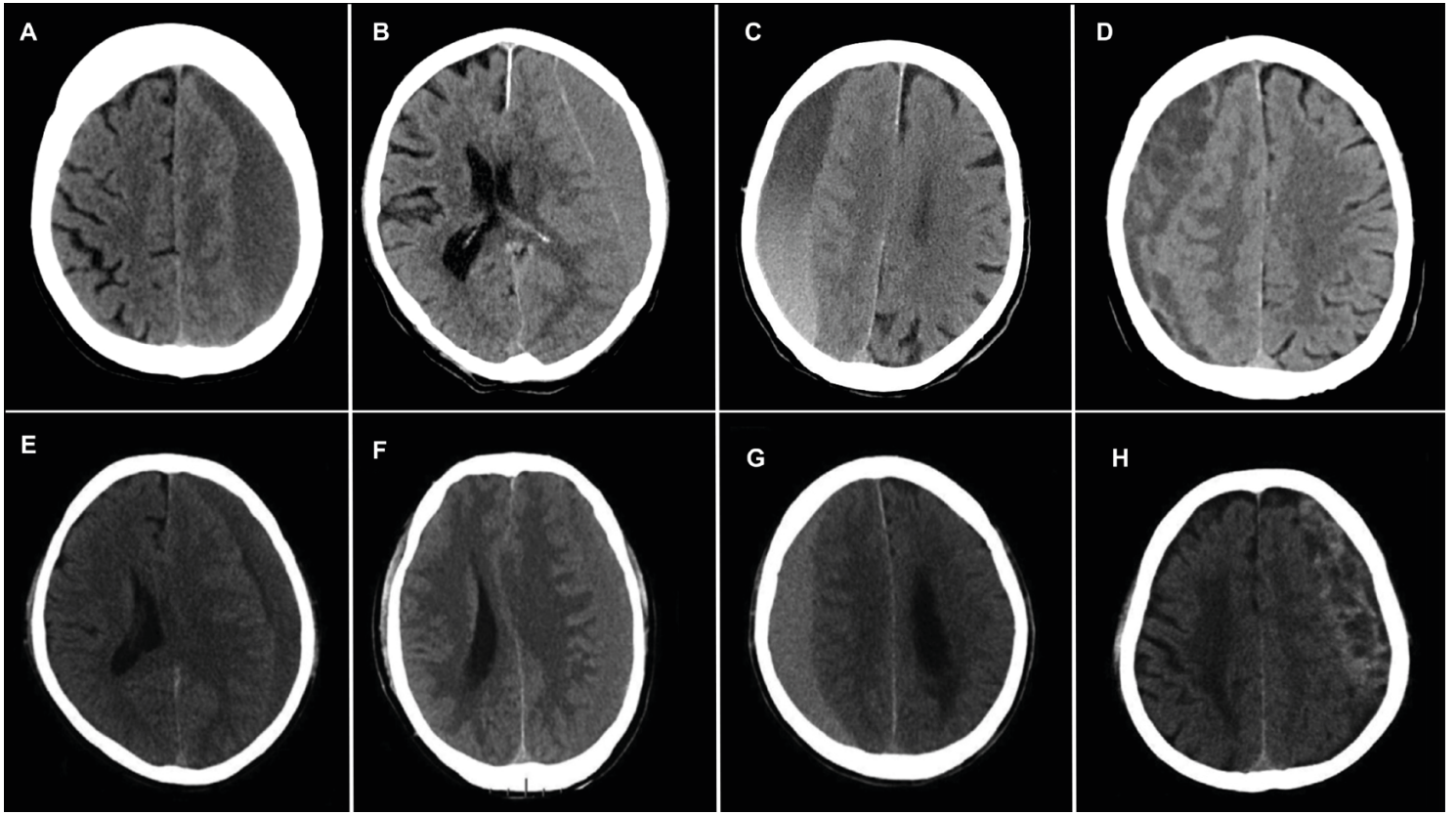

Figure 2. Radiological chronic subdural hematoma subtypes (A-D: achitecture types; E-H: density types). A. Homogeneous hematoma (hypodense type); B. Laminar hematoma; C. Separated hematoma; D. Trabecular hematoma; E. Homogeneous hypodense hematoma; F. Homogeneous isodense hematoma; G. Homogeneous hyperdense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

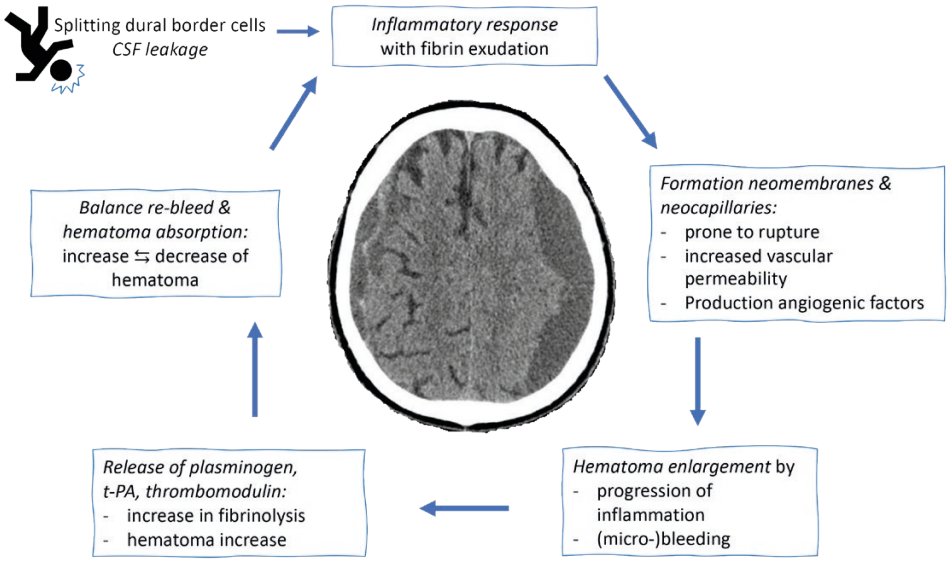

Figure 3. Pathophysiology chronic subdural hematoma – inflammatory cycle

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.

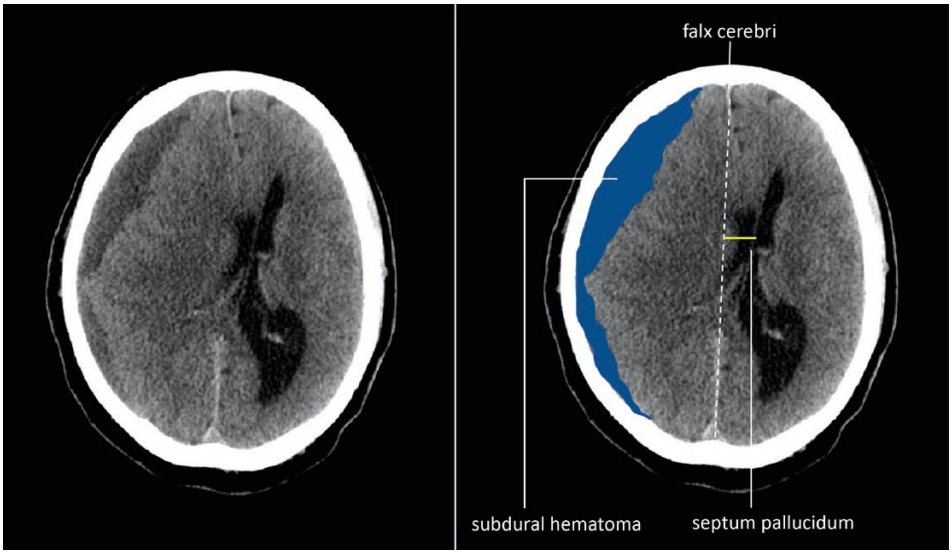

Figure 4. Patient A - CT scan of chronic subdural hematoma at presentation

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.

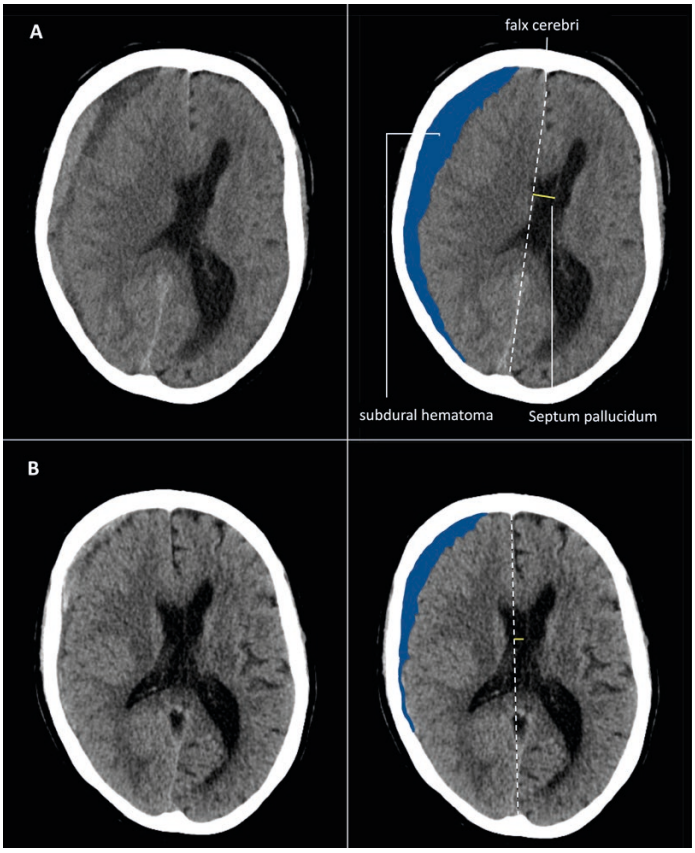

Figure 5. Patient B – CT-scan of chronic subdural hematoma at presentation (A), follow-up (B)

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.

References

1. D'Errico AP, German WJ. Chronic subdural hematoma. Yale J Biol Med 1930;3:11-20.
2. Asghar M, Adhiyaman V, Greenway MW, Bhowmick BK, Bates A. Chronic subdural haematoma in the elderly: A North Wales experience. J R Soc Med. 2002;95:290-292.
3. Adhiyaman V, Asghar M, Ganeshram KN, Bhowmick BK. Chronic subdural haematoma in the elderly. Postgrad Med J 2002;78:71-75.
4. Adhiyaman V, Chattopadhyay I, Irshad F, Curran D, Abraham S. Increasing incidence of chronic subdural haematoma in the elderly. Q J Med 2017;110:375-378.
5. Kudo H, Kuwamura K, Izawa I, Sawa H, Tamaki N. Chronic subdural hematoma in elderly people: present status on Awaji Island and epidemiological prospect. Neurol Med Chir (Tokyo). 1992;32:207-209.
6. Santarius T, Hutchinson PJ. Chronic subdural haematoma: time to rationalize treatment? Br J Neurosurg 2004; 18: 328–32
7. He WS, Velkoff VA, DeBarros KA. 65þ in the U.S. In: U.S. Census Bureau, ed. Current Pop- ulations Reports. Special Studies. Washington, DC: United States Government Printing Office; 2005.
8. Stichting Farmaceutische Kengetallen. Meer geneesmiddelen bij trombose. Pharmaceutisch Weekblad. 2008;143:41.
9. Santarius T, Kirkpatrick PJ, Ganesan D, Chia HL, Jalloh I, Smielewski P, et al. Use of drains versus no drains after burr-hole evacuation of chronic subdural haematoma: a randomised controlled trial. Lancet. 2009;374:1067-1073.
10. Gelabert-Gonzalez M, glesias-Pais M. Garcia- Allut A, Martinez-Rumbo R. Chronic subdural haematoma: surgical treatment and outcome in 1000 cases. Clin. Neurol. Neurosurg 2005; 107:223–229.
11. Mori K, Maeda M. Surgical treatment of chronic subdural hematoma in 500 consecutive cases: clinical characteristics, surgical outcome, complications, and recurrence rate Neurol Med Chir (Tokyo) 2001;8:371-381.
12. Ito H, Maeda M, Uehara T, Yamamoto S, Tamura M, Takashima T. Attenuation Values of Chronic Subdural Haematoma and Subdural Effusion in CT Scans. Acta Neurochirurgica 1984;74:211-217.
13. Markwalder TM. Chronic subdural hematomas: a review. J Neurosurg 1981;54:637–645.
14. Kostanian V, Choi JC, Liker MA, Go JL, Zee CS. Computed tomographic characteristics of chronic subdural hematomas. Neurosurg Clin N Am 2000;11:479-489.
15. Lee KS. The pathogenesis and clinical significance of traumatic subdural hygroma Brain Injury 1998:12;595-60.
16. You-Sub K Sung-Pil J, Dong-Jun S, Sung-Hyun K, Tae-Sun K. Delayed intracranial subdural empyema following burr hole drainage: Case series and literature review. Medicine 2018;97:1-5.
17. Kolias AG, Chari A, Santarius T, Hutchinson PJ. Chronic subdural haematoma: modern management and emerging therapies. Nat Rev Neurol 2014;10, 570-578.
18. Markwalder TM, Steinsiepe KF, Rohner M, Reichenbacj W, Markwalder H. The course of chronic subdural hematomas after burr-hole craniostomy and closed-system drainage. J Neurosurg 1981;55:390-396.
19. Lee KS, Doh JW, Bae HG, Yun IG. Relations among traumatic subdural lesions. J Korean Med Sci 1996;11:55–63.
20. Frati A, Salvati M, Mainiero F, Ippoliti F, Rocchi G, Raco A et al. Inflammation markers and

risk factors for recurrence in 35 patients with a posttraumatic chronic subdural hematoma: a prospective study. J Neurosurg 2004;100:24–32.

21. Gelabert-Gonzalez M, Iglesias-Pais M, Garcia-Allut A, Martinez-Rumbo R. Chronic subdural haematoma: surgical treatment and outcome in 1000 cases. Clin Neurol Neurosurg. 2005;107:223–229.
22. Edlmann E, Giorgi-Coll S, Whitfield PC, Carpenter KLH, Hutchinson PJ. Pathofysiology of chronic subdural hematoma: inflammation, angiogenesis and implications for pharmacotherapy. J of Neuroinflammation 2017;14:1-13
23. Drapkin, AJ. Chronic subdural hematoma: pathophysiological basis for treatment. Br J Neurosurg 1991;5:467–473.
24. Ito H, Komai T, Yamamoto S. Fibrinolytic enzyme in the lining walls of chronic subdural hematoma. J Neurosurg 1978;48:197-200.
25. Labadie EL, Glover D. Local alterations of hemostatic-fibrinolytic mechanisms in reforming subdural hematomas. Neurology 1975; 25: 669-675.
26. Labadie EL, Glover D. Physiopathogenesis of subdural hematomas: part II: inhibition of growth of experi- mental hematomas with dexamethasone. J Neurosurg 1976;45: 393-397.
27. Vaquero J,, Zurita,M, Cincu R. Vascular endothelial growth-permeability factor in granulation tissue of chronic subdural haematomas. Acta Neurochir (Wien) 2002; 144:343- 346.
28. Suzuki K, Takano S, Nose T, Doi M, Ohashi N. Increased concentration of vascular endothelial growth factor (VEGF) in chronic subdural hematoma. J Trauma 1999;46:532-533.
29. Ito H, Saito K, Yamamoto S, Hasegawa T. Tis- sue-type plasminogen activator in the chronic subdural hematoma. Surg Neurol 1988;30:175-179.
30. Saito K, Ito H, Hasegawa T, Yamamoto S. Plasmin-alpha 2-plasmin inhibitor complex and alpha 2-plasmin inhibitor in chronic subdural hematoma. J Neurosurg 1989;70:68-72.
31. Shen J, Yuan L, Ge R, Wang Q, Zhou W, Jiang XC, Shao X. Clinical and radiological factors predicting recurrence of chronic subdural hematoma: a retrospective cohort study. Injury 2019;50:1634–1640.
32. Chon KH, Lee JM, Koh EJ, Choi HY. Independent predic- tors for recurrence of chronic subdural hematoma. Acta Neurochir 2012;154:1541–1548.
33. Yan CY, Huang JW. A reliable nomogram model to predict the recurrence of chronic subdural hematoma after burr hole surgery. World Neurosurgery 2018;118:e356–e366.
34. Ohba SK, Nakagawa T, Murakami H. The risk factors for recurrence of chronic subdural hematoma. Neurosurg Rev 2013;36:145–149.
35. Qian ZY, Sun F, Sun Z. Risk factors for recurrence of chronic subdural hematoma after burr hole surgery: potential protective role of dexamethasone. Br J Neurosurg 2017;31:84–88.
36. Motoie RK, Otsuji R, Ren N, Nagaoka S, Maeda K, Ikai Y et al. Recurrence in 787 Patients with chronic subdural hematoma: retrospective cohort investigation of associated factors including direct oral anticoagulant use. World Neurosurg 2018;118:e87–e91.
37. Motiei-Langroudi RS, Shi S, Adeeb N, Gupta R, Griessenauer CJ, Papavassiliou E et al. Factors predicting reoperation of chronic subdural hematoma following primary surgical evacuation. J Neurosurg 2018;129:1143–1150.
38. www.opendisdata.nl/msz/zorgproduct/972802117
39. Liu W, Bakker NA, Groen RJM. Chronic subdural hematoma: a systematic review and meta¬analysis of surgical procedures. A systematic review. J Neurosurg 2014;121:665–673.
40. Weigel R, Schmiedek P, Krauss JK. Outcome of contemporary surgery for chronic subdural

haematoma: evidence based review. J Neurol Neurosurg Psychiatry 2003;74:937–943.

41. Ivamoto HS, Lemos HP, Atallah AN. Surgical treatments for chronic subdural haematomas: a comprehensive systematic review. World Neurosurg 2016;86:399–418.
42. Thomas PAW, Mitchell PS, Marshman LAG. Early postoperative morbidity after chronic subdural hematoma: predictive usefulness of the physiological and operative severity score for enumeration of mortality and morbidity, American college of surgeons national surgical quality improvement program, and American society of anesthesiologists grade in a prospective cohort. World Neurosurg 2019 Jan 3;pii: S1878-8750(18)32942-5.
43. Rauhala M, Helén P, Huhtala H, Heikkilä P, Iverson GL, Niskakangas T, Öhman J, Luoto TM. Chronic subdural hematoma—incidence, complications, and financial impact. Acta Neurochir 2020:162:2033–2043.
44. Weigel R, Hohenstein A, Schlickum L, Weiss C, Schilling L. Angiotensin converting enzyme inhibition for arterial hypertension reduces the risk of recurrence in patients with chronic subdural hematoma possibly by an antiangiogenic mechanism. Neurosurgery 2007:788–792.
45. Poulsen FR, Munthe S, Søe M, Halle B. Perindopril and residual chronic subdural hematoma volumes six weeks after burr hole surgery: a randomized trial. Clin Neurol Neurosurg 2014;123:4–8.
46. Neidert MC, Schmidt T, Mitova T, Fierstra J, Bellut D, Regli L et al. Preoperative angiotensin converting enzyme inhibitor usage in patients with chronic subdural hematoma: Associations with initial presentation and clinical outcome. J Clin Neurosci. 2016;28:82–86.
47. Bartek J Jr, Sjavik K, Schaible S, Gulati S, Solheim O, Forander P et al. The role of angiotensin-converting enzyme inhibitors in patients with chronic subdural hematoma: A scandinavian population-based multicenter study. World Neurosurg. 2018;113:e555–e60.
48. Bender MB, Christoff N. Nonsurgical treatment of subdural hematomas. Arch Neurol 1974;31:73–79.
49. Pichert G, Henn V. Konservative Therapie chronischer Subduralhämatome. Schweiz Med Wochenschr. 1987;117:1856-1862.
50. Sun TFD, Boet R, Poon WS. Non-surgical pri- mary treatment of chronic subdural haematoma: preliminary results of using dexamethasone. Br J Neurosurg. 2005;19:327-333.
51. Dran G, Berthier F, Fontaine D, Rasenrarijao D, Paquis P. Effectiveness of adjuvant corticosteroid therapy for chronic subdural hematoma: a retrospective study of 198 cases. Neurochirurgie. 2007;53:477-482.
52. Delgado-Lopez PD, Martin-Velasco V, Castilla- Diez JM, Rodriguez-Salazar A, Galacho- Harriero AM, Fernańdez-Arconada O. Dexamethasone treatment in chronic subdural haematoma. Neurocirugiá 2009;20:346-359.
53. Berghauser Pont LM, Dammers R, Schouten JW, Lingsma. Clinical factors associated with outcome in chronic subdural hematoma: a retrospective cohort study of patients on preoperative corticosteroid therapy. Neurosurgery 2012:70;873–880.
54. Chan DYC, Sun TFD, Poon WS. Steroid for chronic subdural hematoma? A prospective phase IIB pilot randomized controlled trial on the use of dexamethasone with surgical drainage for the reduction of recurrence with reoperation. Chinese Neurosurgical Journal 2015;1:1-5.
55. Thotakura AK, Marabathina NR. Nonsurgical Treatment of Chronic Subdural Hematoma with Steroids. World Neurosurg. 2015;84:1968–1972.
56. Prud'homme M, Mathieu F, Marcotte N, Cottin S. A pilot placebo controlled randomized trial of dexamethasone for chronic subdural hematoma. Can J Neu- rol Sci 2016;43:284-290.

57. Fountas K, Kotlia P, Panagiotopoulos V, Fotakopoulos G. The outcome after surgical vs nonsurgical treatment of chronic subdural hematoma with dexamethasone. Interdisciplinary Neurosurgery: Advanced Techniques and Case Management. 2019;16:70-74.
58. Mebberson K, Colditz M, Marshman LAG, Thomas PAW, Mitchell PS, Robertson K. Prospective randomized placebo-controlled double-blind clinical study of adjuvant dexamethasone with surgery for chronic subdural haematoma with post-operative subdural drainage: interim analysis. J Clin Neurosci 2019 Sep 3;pii: S0967-5868(19)31364-5.
59. Hutchinson PJ, Edlmann E, Bulters D, Zolnourian A, Holton P, Suttner N et al. Trial of dexamethasone for chronic subdural hematoma. New Eng J Med 2020;1-12.
60. Wang D, Li T, Tian Y, Wang S, Jin C, Wei H et al. Effects of atorvastatin on chronic subdural hematoma: a preliminary report from three medical centers. J Neurol Sci 2014;336:237–242.
61. Liu H, Liu Z, Liu Y, Kan S, Yang J, Liu H. Effect of atorvastatin on resolution of chronic subdural hematoma: a prospective observational study. J Neurosurg 2016;1-10.
62. Min X, Pin C, Xun Z, Cun-Zu W, Xue-Qiang S, Bo Y. Effects of atorvastatin on conservative and surgical treatments of chronic subdural hematoma in patients. World Neurosurg 2016;91:23–28.
63. Xu M, Chen P, Zhu X, Wang C, Shi X, Yu B.. Effects of atorvastatin on conservative and surgical treatments of chronic subdural hematoma in patients. World Neurosurg 2016:91;23–28.
64. Jiang R, Zhao S, Wang R, Feng H, Zhwang J, Xingang L. Safety and efficacy of atorvastatin for chronic subdural hematoma in chinese patients: a randomized clinical trial. JAMA Neurol 2018;75:1338–1346.
65. Tang R, Shi J, Li X, Zou Y, Wang L, Chen Y et al. Effects of atorvastatin on surgical treatments of chronic subdural hematoma. World Neurosurg 2018;117:e425–e429.
66. Kageyama H, Toyooka T, Tsuzuki N, Oka K. Nonsurgical treatment of chronic subdural hematoma with tranexamic acid. J Neurosurg. 2013;119:332–337.
67. Tanweer O, Frisoli FA, Bravate C, Harrison G, Pacione D, Kondiolka D et al. Tranexamic acid for treatment of residual subdural hematoma after bedside twist- drill evacuation. World Neurosurg. 2016;91:29–33.
68. Yamada T, Natori Y. Prospective study on the efficacy of orally administered tranexamic acid and Goreisan for the prevention of recurrence after chronic subdural hematoma burr hole surgery. World Neurosurg. 2020;134:e549–e553.
69. Kutty RK, Peethambaran AK, Sunilkumar S. Conservative treatment of chronic subdural hematoma in HIV-associated thrombocytopenia with tranexamic acid. J Int Assoc Provid AIDS Care. 2017;16::211–214.
70. Zielinska KA, Van Moortel L, Opdenakker G, De Bosscher K, Van den Steen PE. Endothelial Response to Glucocorticoids in inflammatory Diseases. Front Immunol 2016;7:1-20.
71. Kaal ECA, Vecht CJ. The management of edema in brain tumors. Current Opinion in Oncology 2004;16:593–600.
72. Ellis GL. Subdural hematoma in the elderly. Emerg Med Clin North Am 1990;8:281-294.
73. Lee KS, Bae WK, Bae HG, Doh JW, Yun IG. The computed tomographic attenuation and the age of subdural hematomas. J Korean Med Sci 1997;12:353-359.
74. Sieswerda-Hoogendoorn T, Postema FAM, Verbaan D, Majoie CB, Van Rijn RR. Age determination of subdural hematomas with CT and MRI: a systematic review. Eur J Radiol 2014;83:1257-1268.
75. Scotti G, Terbrugge K, Melancon D, Belanger G. Evaluation of the age of subdural hematomas by computerized tomography. J Neurosurg 1977;47:311-315.
76. Nakaguchi H, Tanishima T, Yoshimasu N. Factors in the natural history of chronic subdural

hematomas that influence their postoperative recurrence. J Neurosurg 2001;95:256-262.

77. Shen J, Yuan L, Ge R, Wang Q, Zhou W, Jiang XC et al. Clinical and radiological factors predicting recurrence of chronic subdural hematoma: a retrospective cohort study. Injury 2019;50:1634–1640.
78. Altaf IS, Vohra AH. Radiolological predictors of recurrence of chronic subdural hematoma. Pak J Med Sci 2018;34:194–197.
79. Chon KH, Lee JM, Koh EJ, Choi HY. Independent predic- tors for recurrence of chronic subdural hematoma. Acta Neurochir 2012;154:1541–1548.
80. Ko BSL, Seo B R, Moon SJ, Kim JH, Kim SH. Clinical analysis of risk factors related to recurrent chronic subdural hema- toma. J Korean Neurosurg Soc 2008;43:11–15.
81. Jung Y, Jung N, El K. Independent predictors for recurrence of chronic subdural hematoma. J Korean Neurosurg Soc 2015;57:266–270.
82. You W, Zhu Y, Wang Y, Liu W, Wang H, Wen L et al. Prevalence of and risk factors for recurrence of chronic subdural hematoma. Acta Neurochir 2018;160:893–899.
83. Yan CY, Huang JW. A reliable nomogram model to predict the recurrence of chronic subdural hematoma after burr hole surgery. World Neurosurg 2018;118:e356–e366.
84. Song DHK, Chun HJ, Yi HJ, Bak KH, Ko Y, Oh SJ. The predicting factors for recurrence of chronic subdural hematoma treated with burr hole and drainage. Korean J Neurotrauma 2014;10:41–48.
85. Huang YHL, Lu CH, Chen WF. Volume of chronic subdural haematoma: is it one of the radiographic factors related to recurrence? Injury 2014;45:327–331.
86. Huang YHY, Lee TC, Liao CC. Bilateral chronic subdural hematoma: what is the clinical significance? Int J Surg 2013;11:544–548 32.
87. Jeong SIK, Won YS, Kwon YJ, Choi CS. Clinical analysis of risk factors for recurrence in patients with chronic subdural hematoma undergoing burr hole trephination. Korean J Neurotrauma 2014;10:15–21.
88. Tugcu B, Tanriverdi O, Baydin S, Hergunsel B, Gunaldi O, Ofluoglu E et al. Can recurrence of chronic subdural hematoma be predicted? A retrospective analysis of 292 cases. J Neurol Surg A Cent Eur Neurosurg 2014;75:37–41.
89. Jang KM, Chou HH, Mun HY, Nam TK, Park YS, Kwon JT. Critical depressed brain volume influences the recurrence of chronic subdural hematoma after surgical evaluation. Nat Res Forum 2020;10:1–8.